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(54) Title: GLYCOPEPTIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

(57) Abstract

Disclosed are derivatives of glycopeptide compounds having at least one substituent of the formula: $-R^a-Y-R^b-(Z)_x$ where R^a, R^b, Y, Z and x are as defined, and pharmaceutical compositions containing such glycopeptide derivatives. The disclosed glycopeptide derivatives are useful as antibacterial agents.

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GLYCOPEPTIDE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Serial No. 60/113,728, filed December 23, 1998; U.S. Serial No. 60/129,313, filed April 14, 1999; U.S. Serial No. 60/164,024, filed November 4, 1999; and U.S. Serial No. 60/169,978, filed December 10, 1999; the disclosures of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel derivatives of glycopeptide antibiotics. This invention also relates to pharmaceutical compositions containing such glycopeptide derivatives, to methods of using such glycopeptide derivatives as antibacterial agents, and to processes for preparing such glycopeptide derivatives.

Background

Glycopeptides are a well-known class of antibiotics produced by various microorganisms. These complex multi-ring peptide compounds are effective antibacterial agents against a majority of Gram-positive bacteria. The use of glycopeptides as antibiotics, however, has been overshadowed by the semi-synthetic penicillins, cephalosporins and lincomycin due to the higher levels of mammalian toxicity observed with the glycopeptides. In recent years, however, bacteria resistant to the penicillins, cephalosporins and the like have emerged resulting in, for example, multiple-resistant and methicillin-resistant staphylococcal (MRS) infections. Glycopeptides, such as vancomycin, are typically effective against such microorganisms and vancomycin has become the

drug of last resort for MRS and other infections. The glycopeptides are believed to be effective against such resistant microorganism because they have a different mode of action than other antibiotics. In this regard, the glycopeptides are believed to selectively inhibit a different step in bacterial cell wall synthesis than the penicillin-type antibiotics.

More specifically, the cell wall of bacteria consists of linear polysaccharide chains cross-linked by short peptides. This arrangement of cross-linked polysaccharides confers mechanical support to the cell wall, thus preventing the bacteria from bursting due to its high internal osmotic pressure. During the synthesis of the bacterial cell wall, cross-linking of the polysaccharides takes place after lipid-linked disaccharide-pentapeptide constructs are incorporated into linear polysaccharide chains by a transglycolase enzyme. The subsequent cross-linking reaction is the last step in the synthesis of the cell wall and is catalyzed by an enzyme known as peptidoglycan transpeptidase.

One method by which antibacterial agents exert their antibacterial activity is by inhibiting the transglycosylase enzyme, thus interfering with the penultimate step in the synthesis of the bacterial cell wall. Although not wishing to be bound by theory, it is believed that glycopeptide antibiotics, such as vancomycin, bind with high affinity and specificity to *N*-terminal sequences (i.e., L-lysyl-D-alanyl-D-alanine in vancomycin-sensitive organisms) of the peptidoglycan precursors (known as lipid intermediate II). By binding to and sequestering these precursors, vancomycin prevents their utilization in cell wall biosynthesis. Thus, vancomycin inhibits the bacterial transglycosylase that is responsible for adding lipid intermediate II subunits to growing peptidoglycan chains. This step of bacterial cell wall synthesis preceeds the cross-linking transpeptidation step which is known to be inhibited by beta-lactams antibiotics. It is also believed that vancomycin inhibits transpeptidation which involves the D-alanyl-D-alanine termini. However,

since this step occurs subsequent to transglycosylation, inhibition of transpeptidation is not directly observed.

A number of derivatives of vancomycin and other glycopeptides are known in the art. For example, see U.S. Patent Nos. 4,639,433; 4,643,987; 4,497,802; 4,698,327; 5,591,714; 5,840,684; and 5,843,889. Other derivatives are disclosed in EP 0 802 199; EP 0 801 075; EP 0 667 353; WO 97/28812; WO 97/38702; WO 98/52589; WO 98/52592; and in *J. Amer. Chem. Soc.*, **1996**, *118*, 13107-13108; *J. Amer. Chem. Soc.*, **1997**, *119*, 12041-12047; and *J. Amer. Chem. Soc.*, **1994**, *116*, 4573-4590. The disclosures of these and other documents referred to throughout this application are incorporated herein by reference in their entirety.

A need exists, however, for glycopeptide derivatives having improved activity, selectivity and reduced mammalian toxicity. Moreover, certain microorganisms are beginning to develop resistance to vancomycin, such as vancomycin-resistant enterococci (VRE). Accordingly, it would be highly desirable to provide novel glycopeptide derivatives which are effective against a broad spectrum of bacteria, including resistant strains such as VRE. Moreover, it would be highly advantageous to provide glycopeptide derivatives having improved antibacterial activity and selectivity, and low mammalian toxicity.

SUMMARY OF THE INVENTION

The present invention provides novel derivatives of glycopeptide antibiotics having improved properties compared to the unsubstituted glycopeptide, including enhanced activity, selectivity and reduced mammalian toxicity. For example, certain vancomycin derivatives of this invention demonstrate greatly enhanced antibacterial activity compared to vancomycin itself. Such vancomycin derivatives are also highly effective against vancomycin-resistant enterococci strains while exhibiting reduced mammalian toxicity.

Accordingly, in one of its composition aspects, this invention provides a glycopeptide compound having at least one substituent of the formula:

$$-R^a-Y-R^b-(Z)_x$$

wherein

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OC(O)-$, $-NR^cSO_2-$, $-OSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, ,$-P(O)(OR^c)O-$, $-P(O)(OR^c)NR^c-$, $-OP(O)(OR^c)O-$,$-OP(O)(OR^c)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$ and $-NR^cSO_2NR^c-$;

each *Z* is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

x is 1 or 2;

and pharmaceutically acceptable salts thereof;

provided that:

(i) when Y is $-NR^c-$, R^c is alkyl of 1 to 4 carbon atoms, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(ii) when Y is $-C(O)NR^c-$, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(iii) when Y is sulfur, Z is hydrogen and R^b is alkylene, then R^b contains at least 7 carbon atoms; and

(iv) when Y is oxygen, Z is hydrogen and R^b is alkylene, then R^b contains at least 11 carbon atoms.

Preferably, the glycopeptide compound is substituted with from 1 to 3 substituents of the formula $-R^a-Y-R^b-(Z)_x$.

Each R^a is preferably independently selected from alkylene having from 1 to 10 carbon atoms, more preferably, from 1 to 6 carbon atoms. In a preferred embodiment, R^a is ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$) or butylene ($-CH_2CH_2CH_2CH_2-$). Still more preferably, R^a is ethylene or propylene.

When Z is hydrogen, R^b is preferably alkylene of from 8 to 12 carbon atoms. Accordingly, in this embodiment, R^b and Z preferably form an *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl or *n*-dodecyl group. When Z is other than hydrogen, R^b is preferably a covalent bond or alkylene of from 1 to 10 carbon atoms. In this embodiment, R^b is preferably, a covalent bond, methylene, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_8-$, $-(CH_2)_9-$ or $-(CH_2)_{10}-$.

Each Y is preferably independently selected from the group consisting of oxygen, sulfur, -S-S-, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OC(O)-$,

$-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$ and $-SO_2NR^c-$. More preferably, Y is oxygen, sulfur, $-NR^c-$ or $-NR^cSO_2-$.

Preferably, each *Z* is independently selected from hydrogen, aryl, cycloalkyl, heteroaryl and heterocyclic. More preferably, *Z* is hydrogen or aryl. When *Z* is aryl, preferred *Z* group include phenyl, substituted phenyl, biphenyl, substituted biphenyl and terphenyl groups. Particularly preferred *Z* groups are phenyl, 4-isobutylphenyl, 4'-chlorobiphenyl-4-yl, 4'-trifluoromethylbiphenyl-4-yl, 4-(naphth-2-yl)phenyl, 4-(2-phenylethynyl)phenyl, 4-(3,4-dichlorobenzyloxy)-phenyl, and *p*-terphenyl.

Preferably, *x* is 1.

Particularly preferred $-R^a-Y-R^b-(Z)_x$ groups of this invention are selected from the group consisting of:

$-CH_2CH_2-NH-(CH_2)_9CH_3$;

$-CH_2CH_2CH_2-NH-(CH_2)_8CH_3$;

$-CH_2CH_2CH_2CH_2-NH-(CH_2)_7CH_3$;

$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$;

$-CH_2CH_2-NHSO_2-(CH_2)_{11}CH_3$;

$-CH_2CH_2-S-(CH_2)_8CH_3$;

$-CH_2CH_2-S-(CH_2)_9CH_3$;

$-CH_2CH_2-S-(CH_2)_{10}CH_3$;

$-CH_2CH_2CH_2-S-(CH_2)_8CH_3$;

$-CH_2CH_2CH_2-S-(CH_2)_9CH_3$;

$-CH_2CH_2CH_2-S-(CH_2)_3-CH=CH-(CH_2)_4CH_3$ (*trans*);

$-CH_2CH_2CH_2CH_2-S-(CH_2)_7CH_3$;

$-CH_2CH_2-S(O)-(CH_2)_9CH_3$;

$-CH_2CH_2-S-(CH_2)_6Ph$;

$-CH_2CH_2-S-(CH_2)_8Ph$;

$-CH_2CH_2CH_2-S-(CH_2)_8Ph$;

$-CH_2CH_2-NH-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2-NH-CH_2$-4-[4-$(CH_3)_2CHCH_2$-]-Ph;

$-CH_2CH_2-NH-CH_2$-4-(4-CF_3-Ph)-Ph;

$-CH_2CH_2-S-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2-S(O)-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2CH_2-S-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2CH_2-S(O)-CH_2$-4-(4-Cl-Ph)-Ph;

$-CH_2CH_2CH_2-S-CH_2$-4-[3,4-di-Cl-PhCH_2O-)-Ph;

$-CH_2CH_2-NHSO_2-CH_2$-4-[4-(4-Ph)-Ph]-Ph;

$-CH_2CH_2CH_2-NHSO_2-CH_2$-4-(4-Cl-Ph)-Ph;

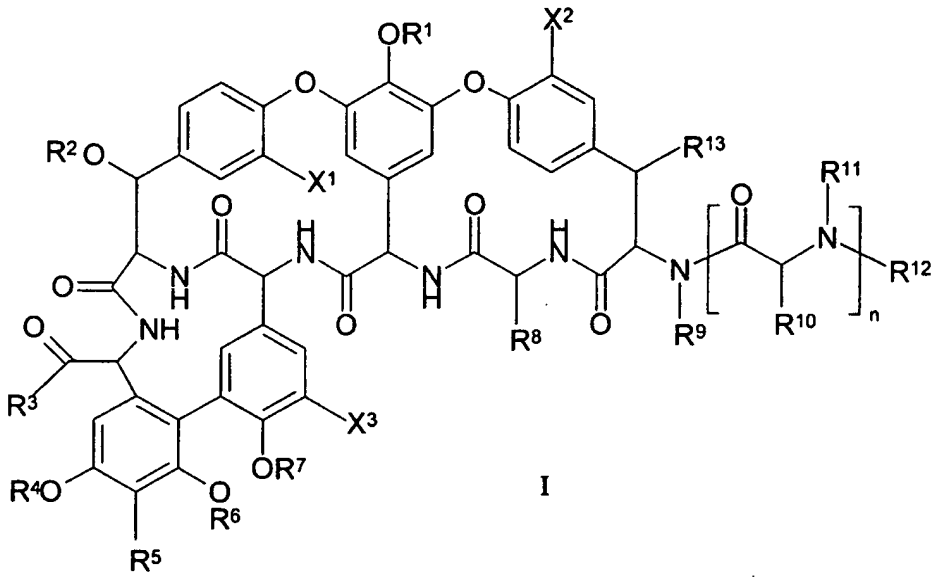
$-CH_2CH_2CH_2-NHSO_2-CH_2$-4-(Ph-C≡C-)-Ph;

$-CH_2CH_2CH_2-NHSO_2$-4-(4-Cl-Ph)-Ph; and

$-CH_2CH_2CH_2-NHSO_2$-4-(naphth-2-yl)-Ph.

Other preferred $-R^a-Y-R^b-(Z)_x$ groups are shown in Tables I-VI below.

In another of its composition aspects, this invention provides a compound of formula I:



I

wherein

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-R^a-Y-R^b-(Z)_x$; or a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$;

R^2 is hydrogen or a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$;

R^3 is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$, $-NR^c-R^a-Y-R^b-(Z)_x$, $-NR^cR^c$, or $-O-R^c$;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, $-C(O)R^d$ and a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$;

R^5 is selected from the group consisting of hydrogen, halo, $-CH(R^c)-NR^cR^c$, $-CH(R^c)-NR^cR^e$ and $-CH(R^c)-NR^c-R^a-Y-R^b-(Z)_x$;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, $-C(O)R^d$ and a saccharide group optionally substituted with $-NR^c-R^a-Y-R^b-(Z)_x$, or R^5 and R^6 can be joined, together with the atoms to which they are attached, form a heterocyclic ring optionally substituted with $-NR^c-R^a-Y-R^b-(Z)_x$;

R^7 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, $-R^a-Y-R^b-(Z)_x$, and $-C(O)R^d$;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^9 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^{10} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic; or R^8 and R^{10} are joined to form $-Ar^1-O-Ar^2-$, where Ar^1 and Ar^2 are independently arylene or heteroarylene;

R^{11} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic, or R^{10} and R^{11} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

R^{12} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $-C(O)R^d$, $-C(NH)R^d$, $-C(O)NR^cR^c$, $-C(O)OR^d$, $-C(NH)NR^cR^c$ and $-R^a-Y-R^b-(Z)_x$, or R^{11} and R^{12} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

R^{13} is selected from the group consisting of hydrogen or $-OR^{14}$;

R^{14} is selected from hydrogen, $-C(O)R^d$ and a saccharide group;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is a saccharide group;

X^1, X^2 and X^3 are independently selected from hydrogen or chloro;

each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, $-P(O)(OR^c)O-$,

$-P(O)(OR^c)NR^c-$, $-OP(O)(OR^c)O-$, $-OP(O)(OR^c)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$ and $-NR^cSO_2NR^c-$;

each *Z* is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2;

x is 1 or 2;

and pharmaceutically acceptable salts, stereoisomers and prodrugs thereof;

provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7 or R^{12} has a substitutent of the formula $-R^a-Y-R^b-(Z)_x$;

and further provided that:

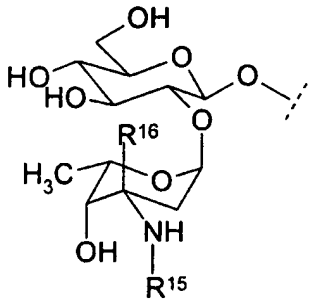
(i) when Y is $-NR^c-$, R^c is alkyl of 1 to 4 carbon atoms, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(ii) when Y is $-C(O)NR^c-$, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(iii) when Y is sulfur, Z is hydrogen and R^b is alkylene, then R^b contains at least 7 carbon atoms; and

(iv) when Y is oxygen, Z is hydrogen and R^b is alkylene, then R^b contains at least 11 carbon atoms.

Preferably, R^1 is a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$. More preferably, R^1 is a saccharide group of the formula:



wherein

R^{15} is $-R^a-Y-R^b-(Z)_x$, where R^a, R^b, Y, *Z* and *x* are as defined herein; and

R^{16} is hydrogen or methyl.

Preferably, R^2 is hydrogen.

R^3 is preferably $-OR^c$ or $-NR^cR^c$; more preferably R^3 is -OH. Particularly preferred R^3 groups are those shown in Tables I-IV as R^{22}.

Preferably, R^4, R^6 and R^7 are each independently selected from hydrogen or $-C(O)R^d$. More preferably, R^4, R^6 and R^7 are each hydrogen.

R^5 is preferably hydrogen, $-CH_2-NHR^c$, $-CH_2-NR^cR^e$ and $-CH_2-NH-R^a-Y-R^b-(Z)_x$, where R^a, R^b, R^c, R^e, Y, *Z* and *x* are as defined herein. Particularly preferred R^5 groups include hydrogen, $-CH_2-N-(N-CH_3-D$-glucamine); $-CH_2-NH-CH_2CH_2-NH-(CH_2)_9CH_3$; $-CH_2-NH-CH_2CH_2-NH-(CH_2)_{11}CH_3$; $-CH_2-NH-(CH_2)_5-COOH$; and $-CH_2-N$-(2-amino-2-deoxygluconic acid). Other preferred R^5 groups are those shown in Table III as R^{23}.

Preferably, R^8 is $-CH_2C(O)NH_2$, $-CH_2COOH$, benzyl, 4-hydroxyphenyl or 3-chloro-4-hydroxyphenyl. More preferably, R^8 is $-CH_2C(O)NH_2$.

R^9 is preferably hydrogen or alkyl. More preferably, R^9 is hydrogen.

R^{10} is preferably alkyl or substituted alkyl. More preferably, R^{10} is the side-chain of a naturally occurring amino acid. Still more preferably, R^{10} is isobutyl.

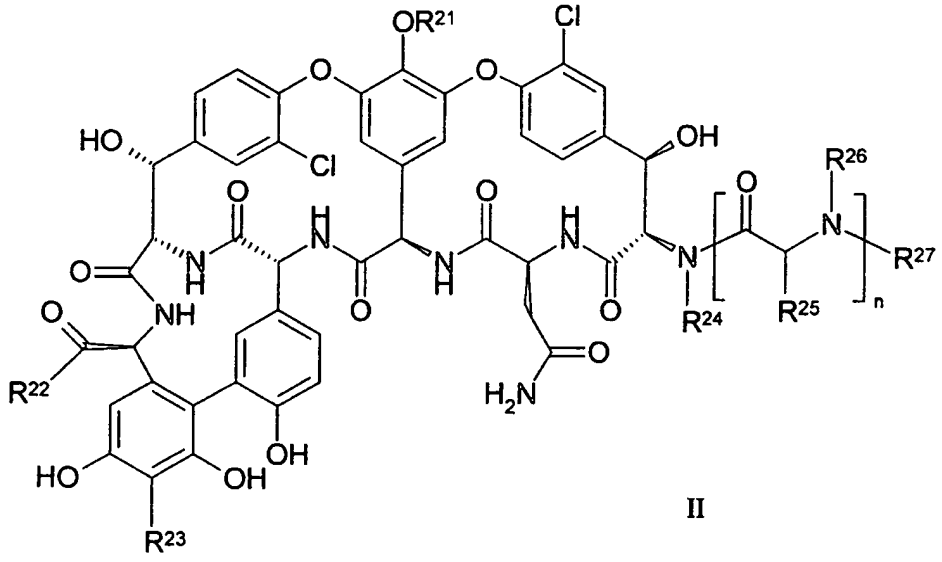
R^{11} is preferably hydrogen or alkyl. More preferably, R^{11} is hydrogen or methyl.

R^{12} is preferably hydrogen, alkyl, substituted alkyl or $-C(O)R^d$. More preferably, R^{12} is hydrogen or $-CH_2COOH$. Other preferred R^{12} groups are those shown in Table II as R^{27}.

X^1 and X^2 are preferably chloro. X^3 is preferably hydrogen.

Preferably, *n* is 0 or 1. More preferably, *n* is 1.

In still another of its composition aspects, this invention provides a compound of formula II:



II

wherein

R^{21} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-R^a-Y-R^b-(Z)_x$; or a saccharide group optionally substituted with $-R^a-Y-R^b-(Z)_x$;

R^{22} is $-OR^c$, $-NR^cR^c$, $-O-R^a-Y-R^b-(Z)_x$ or $-NR^c-R^a-Y-R^b-(Z)_x$;

R^{23} is selected from the group consisting of hydrogen, halo, $-CH(R^c)-NR^cR^c$, $-CH(R^c)-R^e$ and $-CH(R^c)-NR^c-R^a-Y-R^b-(Z)_x$;

R^{24} is selected from the group consisting of hydrogen and lower alkyl;

R^{25} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^{26} is selected from the group consisting of hydrogen and lower alkyl; or R^{25} and R^{26} are joined, together with the carbon and nitrogen atoms to which they are attached, to form a heterocyclic ring;

R^{27} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, $-C(O)R^d$, $-C(NH)R^d$, $-C(O)NR^cR^c$, $-C(O)OR^d$, $-C(NH)NR^cR^c$ and $-R^a-Y-R^b-(Z)_x$, or R^{26} and R^{27} are joined, together with the nitrogen atom to which they are attached, to form a heterocyclic ring;

each R^a is independently selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene;

each R^b is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, alkenylene, substituted alkenylene, alkynylene and substituted alkynylene, provided R^b is not a covalent bond when Z is hydrogen;

each R^c is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic and $-C(O)R^d$;

each R^d is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

R^e is an aminosaccharide group;

each Y is independently selected from the group consisting of oxygen, sulfur, $-S-S-$, $-NR^c-$, $-S(O)-$, $-SO_2-$, $-NR^cC(O)-$, $-OSO_2-$, $-OC(O)-$, $-NR^cSO_2-$, $-C(O)NR^c-$, $-C(O)O-$, $-SO_2NR^c-$, $-SO_2O-$, $-P(O)(OR^e)O-$, $-P(O)(OR^e)NR^c-$, $-OP(O)(OR^e)O-$, $-OP(O)(OR^e)NR^c-$, $-OC(O)O-$, $-NR^cC(O)O-$, $-NR^cC(O)NR^c-$, $-OC(O)NR^c-$ and $-NR^cSO_2NR^c-$;

each *Z* is independently selected from hydrogen, aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic;

n is 0, 1 or 2;

x is 1 or 2;

and pharmaceutically acceptable salts, stereoisomers and prodrugs thereof;

provided that at least one of R^{21}, R^{22}, R^{23} or R^{27} has a substitutent of the formula $-R^a-Y-R^b-(Z)_x$;

and further provided that:

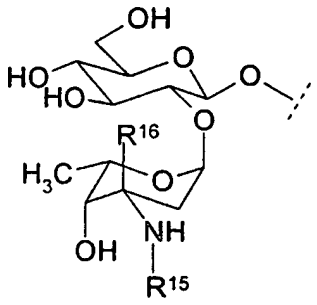
(i) when Y is $-NR^c-$, R^c is alkyl of 1 to 4 carbon atoms, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(ii) when Y is $-C(O)NR^c-$, Z is hydrogen and R^b is alkylene, then R^b contains at least 5 carbon atoms;

(iii) when Y is sulfur, Z is hydrogen and R^b is alkylene, then R^b contains at least 7 carbon atoms; and

(iv) when Y is oxygen, Z is hydrogen and R^b is alkylene, then R^b contains at least 11 carbon atoms.

Preferably, R^{21} is a saccharide group of the formula:



wherein

R^{15} is $-R^a-Y-R^b-(Z)_x$, where R^a, R^b, Y, Z and x are as defined herein; and

R^{16} is hydrogen or methyl.

R^{22} is preferably $-OR^c$ or $-NR^cR^c$; more preferably R^{22} is $-OH$. Particularly preferred R^{22} groups are those shown in Tables I-IV.

R^{23} is preferably hydrogen, $-CH_2-R^e$, $-CH_2-NHR^c$ and $-CH_2-NH-R^a-Y-R^b-(Z)_x$, where R^a, R^b, R^c, R^e, Y, Z and x are as defined herein. Particularly preferred R^{23} groups include hydrogen, $-CH_2$-*N*-(*N*-CH_3-D-glucamine); $-CH_2-NH-CH_2CH_2-NH-(CH_2)_9CH_3$; $-CH_2-NH-CH_2CH_2-NH-(CH_2)_{11}CH_3$; $-CH_2-NH-(CH_2)_5-COOH$; and $-CH_2$-*N*-(2-amino-2-deoxygluconic acid). Other preferred R^{23} groups are shown in Table III.

R^{24} is preferably hydrogen or alkyl. More preferably, R^{24} is hydrogen.

R^{25} is preferably alkyl or substituted alkyl. More preferably, R^{25} is the side-chain of a naturally occurring amino acid. Still more preferably, R^{25} is isobutyl.

R^{26} is preferably hydrogen or alkyl. More preferably, R^{26} is hydrogen or methyl.

R^{27} is preferably hydrogen, alkyl, substituted alkyl or $-C(O)R^d$. More preferably, R^{27} is hydrogen or $-CH_2COOH$. Other preferred R^{27} groups are those shown in Table II.

In yet another of its composition aspects, this invention provides a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically effective amount of a glycopeptide compound having at least one substituent of the formula:

$$-R^a-Y-R^b-(Z)_x$$

wherein R^a, R^b, Y, Z and x are as defined herein.

Additionally, this invention provides a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a therapeutically effective amount of a compound of formula I or II.

The compounds of this invention are highly effective antibacterial agents. Accordingly, in one of its method aspects, this invention provides a method of treating a mammal having a bacterial disease, the method comprising administering to the mammal a therapeutically effective amount of a glycopeptide compound having at least one substituent of the formula:

$$-R^a-Y-R^b-(Z)_x$$

wherein R^a, R^b, Y, Z and x are as defined herein.

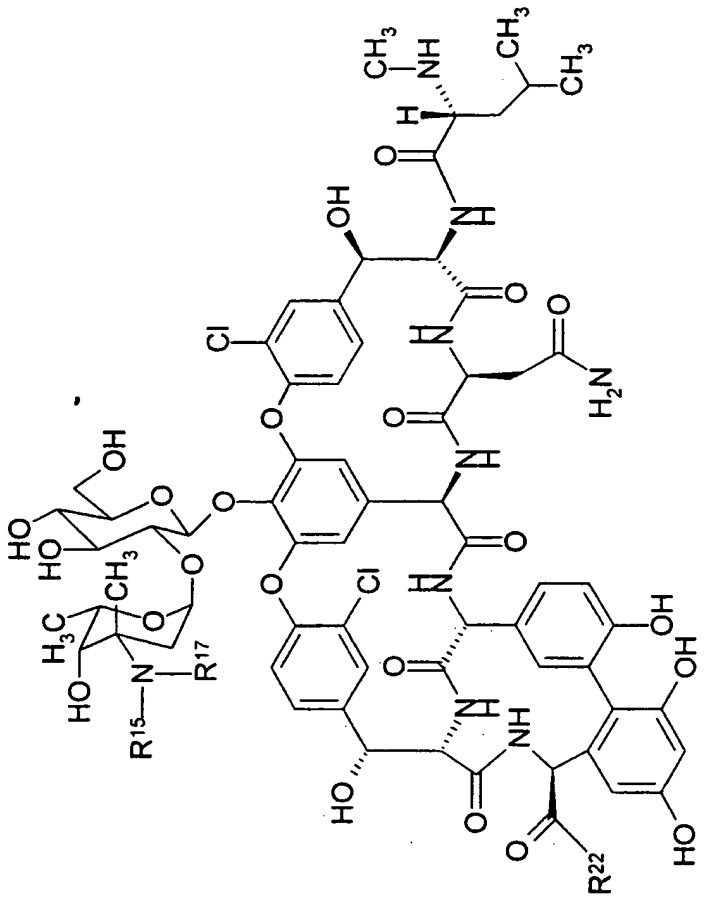
Additionally, this invention provides a method of treating a mammal having a bacterial disease, the method comprising administering to the mammal a therapeutically effective amount of a compound of formula I or II.

This invention also provides processes for preparing glycopeptide derivatives, which processes are described further herein below.

In another of its aspects, this invention is directed to the use of a glycopeptide derivative of formula I or formula II in the manufacture of a formulation or medicament for a medicinal treatment. Preferably, the formulation or medicament is used as an antibacterial agent.

Preferred compounds of this invention are those set forth in the following tables as formulas III, IV, V, VI, VII and VIII, and pharmaceutically-acceptable salts thereof:

Table I



III

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
1	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH
2	$-CH_2CH_2-N[(CH_2)_9CH_3]_2$	-OH
3	$-CH_2CH_2-NH-(CH_2)_7CH_3$	-OH
4	$-CH_2CH_2-NH-(CH_2)_5CH_3$	-OH
5	$-CH_2CH_2-NH-CH_2Ph$	-OH
6	$-CH_2CH_2-NH-CH_2$-4-Ph-Ph	-OH
7	$-CH_2CH_2-NH-CH_2$-4-(4-Cl-Ph)-Ph	-OH
8	$-CH_2CH_2-NH-(CH_2)_8CH_3$	-OH
9	$-CH_2CH_2-NH-CH_2$-cyclohexyl	-OH
10	$-CH_2CH_2CH_2-NH-(CH_2)_8CH_3$	-OH
11	$-CH_2CH_2CH_2CH_2-NH-(CH_2)_7CH_3$	-OH
12	$-CH_2CH_2CH_2CH_2CH_2-NH-(CH_2)_6CH_3$	-OH
13	$-CH_2CH_2-N(CH_3)-(CH_2)_9CH_3$	-OH
14	$-CH_2CH_2-NH-(CH_2)_3CH=CH(CH_2)_4CH_3$ (*trans*)	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
15	$-CH_2CH_2-NH-CH_2CH=C(CH_3)(CH_2)_2-CH=C(CH_3)_2$ (*trans, trans*)	-OH
16	$-CH_2CH_2-NH-(CH_2)_8CH(OH)CH_3$	-OH
17	$-CH_2CH_2-NH-(CH_2)_8CH=CH_2$	-OH
18	$-CH_2CH_2-NH-CH_2$-cyclopropyl	-OH
19	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3N(CH_3)_2$
20	$-CH_2CH_2-N[(CH_2)_9CH_3]_2$	$-NH(CH_2)_3N(CH_3)_2$
21	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-(D-glucosamine)
22	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-NHCH(COOH)CH_2COOH
23	$-CH_2CH_2-NH-CH_2$-4-(4-Cl-Ph)-Ph	-*N*-(D-glucosamine)
24	$-CH_2CH_2-NH-(CH_2)_8CH_3$	-*N*-(D-glucosamine)
25	$-CH_2CH_2-NH-CH_2CH=C(CH_3)(CH_2)_2-CH=C(CH_3)_2$ (*trans, trans*)	-*N*-(D-glucosamine)
26	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-NHCH(CO_2CH_3)$CH_2CO_2CH_3$
27	$-CH_2CH_2-NH-(CH_2)_8CH(OH)CH_3$	-NHCH(COOH)CH_2COOH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
28	$-CH_2CH_2-NHC(O)-(CH_2)_6CH(CH_3)CH_3$	-OH
29	$-CH_2CH_2-NHC(O)-(CH_2)_8CH_3$	-OH
30	$-CH_2CH_2-OC(O)-(CH_2)_8CH_3$	-OH
31	$-CH_2-C(O)O-(CH_2)_9CH_3$	-OH
32	$-CH_2-C(O)NH-(CH_2)_9CH_3$	-OH
33	$-CH_2-C(O)O-(CH_2)_7CH_3$	-OH
34	$-CH_2CH_2-NHSO_2-(CH_2)_7CH_3$	-OH
35	$-CH_2CH_2-OSO_2-(CH_2)_7CH_3$	-OH
36	$-CH_2CH_2-S-(CH_2)_9CH_3$	-OH
37	$-CH_2CH_2-NHC(O)-(CH_2)_6CH_3$	-OH
38	$-CH_2CH_2-NHC(O)-(CH_2)_7CH_3$	-OH
39	$-CH_2CH_2-NHC(O)-(CH_2)_9CH_3$	-OH
40	$-CH_2-C(O)NH-(CH_2)_6CH_3$	-OH
41	$-CH_2-C(O)NH-(CH_2)_7CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
42	$-CH_2-C(O)NH-(CH_2)_8CH_3$	-OH
43	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3$-morpholin-4-yl
44	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3-NH-(CH_2)_2CH_3$
45	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_2$-piperidin-1-yl
46	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_4NHC(N)NH_2$
47	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_2-N^+(CH_3)_3$
48	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)(CH_2)_3NHC(N)NH_2$
49	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH[(CH_2)_3NH-]_3H$
50	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-N[(CH_2)_3N(CH_3)_2]_2$
51	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3$-imidiazol-1-yl
52	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH_2$-4-pyridyl
53	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3CH_3$
54	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_2OH$
55	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_5OH$

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
56	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_2OCH_3$
57	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH_2$-tetrahydrofuran-2-yl
58	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-N[(CH_2)_2OH]_2$
59	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_2N[(CH_2)_2OH]_2$
60	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-(glucamine)
61	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH_2COOH$
62	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2OH$
63	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_2COOH$
64	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3SO_3H$
65	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)(CH_2)_3COOH$
66	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)(CH_2)_2NH_2$
67	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)(CH_2)_3NH_2$
68	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2CO_2(CH_2)_3-N^+(CH_3)_3$
69	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2CO_2-(CH_2)_2C(O)N(CH_3)_2$

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
70	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2CO_2-(CH_2)_3$-morpholin-4-yl
71	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2CO_2(CH_2)_2OC(O)C(CH_3)_3$
72	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(CH_2COOH)CO_2(CH_2)_3-N^+(CH_3)_3$
73	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(CH_2COOH)CO_2(CH_2)_2C(O)N(CH_3)_2$
74	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(CH_2COOH)CO_2(CH_2)_3$-morpholin-4-yl
75	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(CH_2COOH)CO_2(CH_2)_2OC(O)C(CH_3)_3$
76	$-CH_2CH_2-NH-(CH_2)_6Ph$	-OH
77	$-CH_2CH_2-NH-(CH_2)_8Ph$	-OH
78	$-CH_2CH_2-NH-CH_2Ph$	-OH
79	$-CH_2CH_2-NH-CH_2$-4-Cl-Ph	-OH
80	$-CH_2CH_2-NH-CH_2$-4-$[CH_3(CH_2)_2O-]Ph$	-OH
81	$-CH_2CH_2-NH-CH_2$-4-$[CH_3(CH_2)_4O-]Ph$	-OH
82	$-CH_2CH_2-NH-CH_2$-4-$[CH_3(CH_2)_6O-]Ph$	-OH
83	$-CH_2CH_2-NH-CH_2$-4-$[CH_3(CH_2)_8O-]Ph$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
84	$-CH_2CH_2-NH-CH_2$-4-[$CH_3(CH_2)_2$-]Ph	-OH
85	$-CH_2CH_2-NH-CH_2$-4-[$CH_3(CH_2)_3$-]Ph	-OH
86	$-CH_2CH_2-NH-CH_2$-4-[$CH_3(CH_2)_4$-]Ph	-OH
87	$-CH_2CH_2-NH-CH_2$-4-(PhO-)Ph	-OH
88	$-CH_2CH_2-NH-CH_2$-4-(PhS-)Ph	-OH
89	$-CH_2CH_2-NH-CH_2$-3-(PhO-)Ph	-OH
90	$-CH_2CH_2-NH-CH_2$-4-(cyclohexyl-)Ph	-OH
91	$-CH_2CH_2-NH-CH_2$-4-{4-[$CH_3(CH_2)_4O$-]-Ph}-Ph	-OH
92	$-CH_2CH_2-NH-CH_2$-4-CF_3-Ph	-OH
93	$-CH_2CH_2-NH-CH_2$-4-($PhCH_2O$-)Ph	-OH
94	$-CH_2CH_2-NH-CH_2$-4-(4-CH_3-$PhCH_2O$-)Ph	-OH
95	$-CH_2CH_2-NH-(CH_2)_7CH(CH_3)_2$	-OH
96	$-(CH_2)_5-NH-(CH_2)_6CH_3$	-OH
97	$-(CH_2)_3-NH-(CH_2)_9CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
98	$-(CH_2)_4-NH-(CH_2)_9CH_3$	-OH
99	$-(CH_2)_5-NH-(CH_2)_9CH_3$	-OH
100	$-CH_2CH_2-NH-(CH_2)_7CH_3$	-OH
101	$-CH_2CH_2-NH-CH_2$-cyclohexyl	-OH
102	$-CH_2CH_2-S-(CH_2)_7CH_3$	-OH
103	$-CH_2CH_2-OC(O)-(CH_2)_6CH_3$	-OH
104	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	-OH
105	$-CH_2CH_2-OSO_2-(CH_2)_9CH_3$	-OH
106	$-CH_2CH_2-NH-CH_2CH=CH-CH=CH(CH_2)_4CH_3$ (*trans, trans*)	-OH
107	$-CH_2CH_2-NH-CH_2CH=CH-CH=CH(CH_2)_3CH_3$ (*trans, trans*)	-OH
108	$-CH_2CH_2-NH-CH_2CH=CH-CH=CHCH_2CH_3$ (*trans, trans*)	-OH
109	$-CH_2CH_2-NH-CH_2CH=CH-CH_2CH_2CH=CHCH_2CH_3$ (*trans, trans*)	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
110	$-CH_2CH_2-NH-CH_2$-4-Cl-Ph	-OH
111	$-CH_2CH_2-NH-CH_2$-4-($PhCH_2O$-)Ph	-OH
112	$-CH_2CH_2-NH-CH_2$-4-(4-CH_3-$PhCH_2O$-)Ph	-OH
113	$-CH_2CH_2-NH-CH_2$-4-(4-Cl-$PhCH_2O$-)Ph	-OH
114	$-CH_2CH_2-NH-CH_2$-4-[$CH_3(CH_2)_2O$-]Ph	-OH
115	$-CH_2CH_2-NH-CH_2$-4-[$CH_3(CH_2)_4O$-]Ph	-OH
116	$-CH_2CH_2-NH-CH_2$-4-[$CH_3(CH_2)_6O$-]Ph	-OH
117	$-CH_2CH_2-NH-CH_2$-4-[$CH_3(CH_2)_8O$-]Ph	-OH
118	$-CH_2CH_2-NH-CH_2$-4-[$(CH_3)_2CHCH_2$-]Ph	-OH
119	$-CH_2CH_2-NH-CH_2$-4-(Ph-S-)Ph	-OH
120	$-CH_2CH_2-NH-CH_2-4-(4-CF_3-Ph)-Ph$	-OH
121	$-CH_2CH_2-NH-CH_2$-4-{4-[$CH_3(CH_2)_4O$-]-Ph}-Ph	-OH
122	$-CH_2CH_2-NH-(CH_2)_6Ph$	-OH
123	$-CH_2CH_2-NH-(CH_2)_8Ph$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
124	$-CH_2CH_2-NH-(CH_2)_9CH_3$ R^{17} = $-CH_2COOH$	-OH
125	$-CH_2CH_2-NH-(CH_2)_9CH_3$ R^{17} = $-CH_2[CH(OH)]_4COOH$	-OH
126	$-CH_2CH_2-NH-(CH_2)_9CH_3$ R^{17} = $-CH_2$-(imidazol-4-yl)	-OH
127	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3CH_3$
128	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2OH$
129	$-CH_2CH_2-NH-CH_2CH_2$-(cyclopropyl)	-OH
130	$-CH_2-C(O)O-(CH_2)_7CH_3$	-OH
131	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2CO_2CH_3$
132	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(CH_2COOH)CO_2(CH_2)_2N(CH_3)_2$
133	$-CH_2CH_2-NH-CH_2CH=CH-CH=CHCH_3$ (*trans, trans*)	-OH
134	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2CO_2CH_2C(O)N(CH_3)_2$
135	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(CH_2COOH)CO_2CH_2C(O)N(CH_3)_2$
136	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(CH_2COOH)CO_2CH_3$
137	$-CH_2CH_2-NHC(O)-CH_2CH_2-C(O)NHCH_2CH_2NH_2$	$-NHCH_2CH_2CH_2N(CH_3)_2$

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
138	$-CH_2CH_2-NHSO_2-4$-Ph-Ph	-OH
139	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH_2CH_2CO_2CH_3$
140	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH[CH_2CO_2CH_2C(O)N(CH_3)_2]CO_2CH_2$-C(O)-$N(CH_3)_2$
141	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH_2CO_2CH_3$
142	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-(methyl 3-amino-3-deoxyamnnopyranoside)
143	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-(methyl 3-amino-2,3-6-trideoxyhexopyranoside)
144	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-[2-amino-2-deoxy-6-(dihydrogen phosphate)glucopyranose
145	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-(2-amino-2-deoxygluconic acid)
146	$-CH_2CH_2-N(C(O)CH_2NHCH_3)-(CH_2)_9CH_3$	-OH
147	$-CH_2CH_2-N(C(O)CH_3)-(CH_2)_9CH_3$	-OH
148	$-CH_2CH_2-S(O)-(CH_2)_9CH_3$	-OH
149	$-CH_2CH_2-NH-(CD_2)_9CD_3$	-OH
150	$-CH_2CH_2-N(CH_2COOH)-(CH_2)_9CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
151	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_4COOH$
152	$-CH_2CH_2-NHSO_2$-4-(4-Cl-Ph)-Ph	-OH
153	$-CH_2CH_2-N(CH_2CO_2CH_3)-(CH_2)_9CH_3$	-OH
154	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-(*N*-CH_3-D-glucamine)
155	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_6COOH$
156	$-CH_2-C(O)O-CH_2CH_3$	-OH
157	$-CH_2CH_2-S(O)-(CH_2)_7CH_3$	-OH
158	$-CH_2CH_2-NHSO_2$-3-(4-Cl-Ph)-Ph	-OH
159	$-CH_2CH_2-NHSO_2-(CH_2)_7CH_3$	-OH
160	$-CH_2CH_2CH_2-NHSO_2$-4-(4-Cl-Ph)-Ph	-OH
161	$-CH_2CH_2-NH-CH_2$-4-(4-Cl-PhCH_2O-)-Ph	-*N*-(D-glucosamine)
162	$-CH_2CH_2-NH-CH_2$-4-(4-Cl-PhCH_2O-)-Ph	$-NHCH(COOH)CH_2COOH$
163	$-CH_2CH_2-NHSO_2$-4-(naphth-2-yl)-Ph	-OH
164	$-CH_2CH_2-NH-(CH_2)_{11}CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
165	$-CH_2CH_2-N[C(O)CH(NH_2)(CH_2)_4NH_2]-(CH_2)_9CH_3$ (R isomer)	-OH
166	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	-*O*-(D-glucose)
167	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	$-N[(CH_2)_2OH]_2$
168	$-CH_2CH_2CH_2-NH-CH_2-4-(4-CF_3-Ph)-Ph$	-*O*-(D-glucose)
169	$-CH_2CH_2CH_2-NH-CH_2-4-(4-CF_3-Ph)-Ph$	$-N[(CH_2)_2OH]_2$
170	$-CH_2CH_2CH_2-NH-CH_2-4-(4-CF_3-Ph)-Ph$	-OH
171	$-CH_2CH_2CH_2-NH-CH_2-4-(4-CH_3O-Ph)-Ph$	-OH
172	$-CH_2CH_2-NH-CH_2-4-[(CH_3)_3CO]-Ph$	-OH
173	$-CH_2CH_2-NH-CH_2-3,4-di-(CH_3CH_2O)-Ph$	-OH
174	$-CH_2CH_2-NH-CH_2-4-[(CH_3)_2CH]-Ph$	-OH
175	$-CH_2CH_2-NH-CH_2-4-[CH_3(CH_2)_3C\equiv C]-Ph$	-OH
176	$-CH_2CH_2-NH-CH_2-4-[(CH_3)_2CHO]-Ph$	-OH
177	$-CH_2CH_2-NH-CH_2-4-(PhC\equiv C)-Ph$	-OH
178	$-CH_2CH_2-NH-CH_2-4-[(CH_3)_3C]-Ph$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
179	$-CH_2CH_2-NH-CH_2-5-(PhC\equiv C)$-thiophen-2-yl	-OH
180	$-CH_2CH_2-NH-CH_2$-4-(PhCH=CH-)Ph (*trans*)	-OH
181	$-CH_2CH_2-NH-CH_2-(CH=CH)_4-CH_3$ (*trans, trans, trans, trans*)	-OH
182	$-CH_2CH_2-N(C(O)Ph)-(CH_2)_9CH_3$	-OH
183	$-CH_2CH_2-NH-CH_2-4-[4-(CH_3)_3C$-thiazol-2-yl]-Ph	-OH
184	$-CH_2CH_2-N[(CH_2)_9CH_3]-C(O)CH_2$-S-4-pyridyl	-OH
185	$-CH_2CH_2-N[(CH_2)_9CH_3]-C(O)$-2-[PhCH($CH_3$)NHC(O)-]Ph (R isomer)	-OH
186	$-CH_2CH_2-N[(CH_2)_9CH_3]-C(O)$-(1-$PhCH_2OC(O)$-2-oxoimidazolidin-5-yl) (S isomer)	-OH
187	$-CH_2CH_2-N[(CH_2)_9CH_3]-C(O)$-1-HO-cyclopropyl	-OH
188	$-CH_2CH_2-N(C(O)CH_2$-naphth-2-yl)-$(CH_2)_9CH_3$	-OH
189	$-CH_2CH_2-N[C(O)(CH_2)_9CH_2OH]-(CH_2)_9CH_3$	-OH
190	$-CH_2CH_2-N[C(O)CH_2(OCH_2CH_2)_2OCH_3]-(CH_2)_9CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
191	$-CH_2CH_2-N[C(O)CH_2CH(Ph)_2]-(CH_2)_9CH_3$	-OH
192	$-CH_2CH_2-N(C(O)CH_2$-3-HO-Ph)$-(CH_2)_9CH_3$	-OH
193	$-CH_2CH_2-N(C(O)CH_2-NHC(O)$-3-$CH_3$-Ph)$-(CH_2)_9CH_3$	-OH
194	$-CH_2CH_2-N(C(O)CH_2CH_2$-O-Ph)$-(CH_2)_9CH_3$	-OH
195	$-CH_2CH_2-N(C(O)CH_2CH_2$-3-pyridyl)$-(CH_2)_9CH_3$	-OH
196	$-CH_2CH_2-N(C(O)(CH_2)_3$-4-CH_3O-Ph)$-(CH_2)_9CH_3$	-OH
197	$-CH_2CH_2-N(C(O)$-indol-2-yl)$-(CH_2)_9CH_3$	-OH
198	$-CH_2CH_2-N\{C(O)$-1-$[CH_3COC(O)-]$-pyrrolidin-2-yl$\}-(CH_2)_9CH_3$	-OH
199	$-CH_2CH_2-N(C(O)CH_2-NHC(O)-CH=CH$-furan-2-yl)$-(CH_2)_9CH_3$ (*trans*)	-OH
200	$-CH_2CH_2-N[C(O)$-1-CH_3CH_2-7-CH_3-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl]$-(CH_2)_9CH_3$	-OH
201	$-CH_2CH_2-N(C(O)$-1,3-benzodioxol-5-yl)$-(CH_2)_9CH_3$	-OH
202	$-CH_2CH_2-N(C(O)CH_2$-4-oxo-2-thiooxothiazolidin-3-yl)$-(CH_2)_9CH_3$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
203	$-CH_2CH_2-N(C(O)$-3,4,5-tri-HO-cyclohex-1-en-1-yl)-$(CH_2)_9CH_3$ (R,S,R isomer)	-OH
204	$-CH_2CH_2-N(C(O)CH_2CH_2C(O)NH_2)-(CH_2)_9CH_3$	-OH
205	$-CH_2CH_2-N(C(O)CH_2$-5-CH_3-2,4-dioxo-3,4-dihydropyrimidin-1-yl)-$(CH_2)_9CH_3$	-OH
206	$-CH_2CH_2-N(C(O)CH=CH$-imidazol-4-yl)-$(CH_2)_9CH_3$ (*trans*)	-OH
207	$-CH_2CH_2-N[C(O)CH(CH_2CH_2C(O)NH_2)-NHC(O)O-CH_2Ph]-(CH_2)_9CH_3$ (S isomer)	-OH
208	$-CH_2CH_2-N[C(O)CH(CH_2OH)NHC(O)O-CH_2Ph]-(CH_2)_9CH_3$ (S isomer)	-OH
209	$-CH_2CH_2-N[C(O)CH[CH(OH)CH_3]NH-C(O)O-CH_2Ph]-(CH_2)_9CH_3$ (S isomer)	-OH
200	$-CH_2CH_2-N(C(O)CH_2NHSO_2$-4-$CH_3$-Ph)-$(CH_2)_9CH_3$	-OH
211	$-CH_2CH_2-N(C(O)(CH_2)_3-NH_2)-(CH_2)_9CH_3$	-OH
212	$-CH_2CH_2-N(C(O)$-pyrrolidin-2-yl)-$(CH_2)_9CH_3$ (R isomer)	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
213	$-CH_2CH_2-N(C(O)$-pyrrolidin-2-yl$)-(CH_2)_9CH_3$ (S isomer)	-OH
214	$-CH_2CH_2-N(C(O)CH(NH_2)(CH_2)_4-NH_2)-(CH_2)_9CH_3$ (S isomer)	-OH
215	$-CH_2CH_2-N(C(O)CH(NH_2)CH_2$-3-HO-Ph$)-(CH_2)_9CH_3$	-OH
216	$-CH_2CH_2-N(C(O)CH(NH_2)CH_3)-(CH_2)_9CH_3$ (R isomer)	-OH
217	$-CH_2CH_2-N[C(O)CH(CH_2OH)NHC(O)-CH_3]-(CH_2)_9CH_3$ (S isomer)	-OH
218	$-CH_2CH_2-N[C(O)CH(NHC(O)CH_3)-(CH_2)_3-NHC(NH)NH_2]-(CH_2)_9CH_3$ (S isomer)	-OH
219	$-CH_2CH_2-N(C(O)CH_2NHC(O)CH_3)-(CH_2)_9CH_3$	-OH
220	$-CH_2CH_2-N(C(O)CH(CH_3)OC(O)CH-(NH_2)CH_3)-(CH_2)_9CH_3$ (R,R isomer)	-OH
221	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_3OC(O)CH(NH_2)CH_3$
222	$-CH_2CH_2-N(C(O)$-5-oxopyrrolidin-2-yl$)-(CH_2)_9CH_3$ (R isomer)	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
223	$-CH_2CH_2-NHC(O)-CH_2CH(CH_2CH_2Ph)-\{3-[4-(9H\text{-fluroen-}9\text{-}ylCH_2OC(O)NH(CH_2)_4-]-1,4\text{-dioxohexahydro-}1,2-\alpha\text{-pyrazin-}2\text{-}yl\}$ (S,S,S isomer)	-OH
224	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NH(CH_2)_4CH(C(O)\text{-}2\text{-HOOC-pyrrolidin-}1\text{-}yl)NHCH(COOH)-CH_2CH_2Ph$ (S,S isomer)
225	$-CH_2CH_2-NHSO_2-4-(2\text{-Cl-Ph})\text{-Ph}$	-OH
226	$-CH_2CH_2-NHSO_2-4-[4-(CH_3)_3C\text{-Ph}]\text{-Ph}$	-OH
227	$-CH_2CH_2-NHSO_2-4-[4-(Ph)\text{-Ph-}]Ph$	-OH
228	$-CH_2CH_2-NH-4-(4-CF_3\text{-Ph})\text{-Ph}$	-OH
229	$-CH_2CH_2-S-(CH_2)_8Ph$	-OH
230	$-CH_2CH_2-S-(CH_2)_3CH=CH(CH_2)_4CH_3$ (*trans*)	-OH
231	$-CH_2CH_2-S-CH_2CH_2(CF_2)_5CF_3$	-OH
232	$-CH_2CH_2-S-CH_2\text{-}4\text{-}[(CH_3)_2CHCH_2\text{-}]Ph$	-OH
233	$-CH_2CH_2-S-(CH_2)_{11}CH_3$	-OH
234	$-CH_2CH_2-S-(CH_2)_8CH_3$	-OH

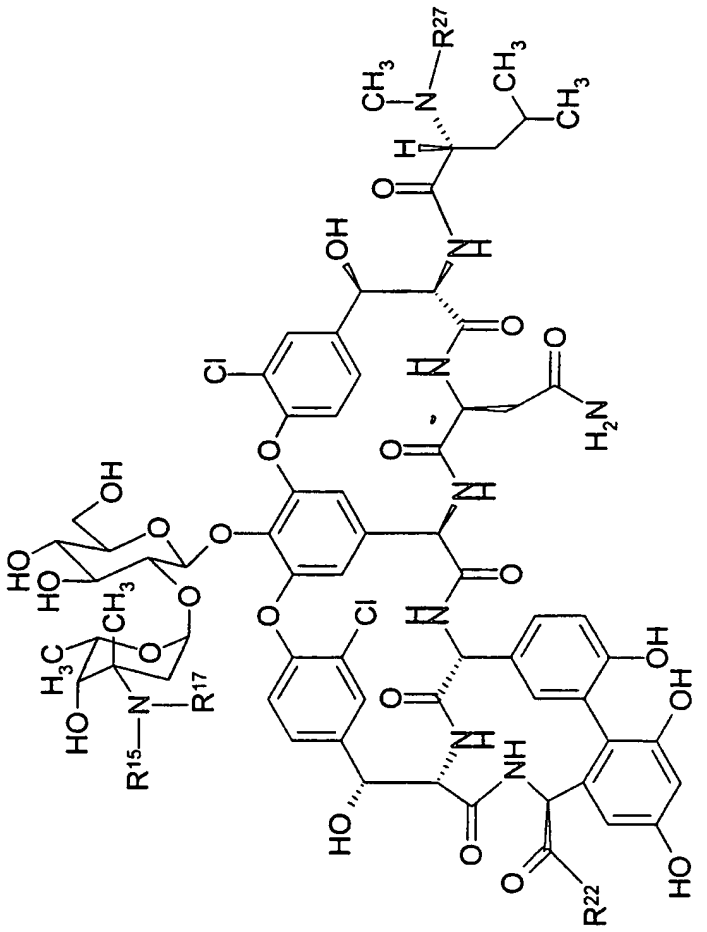
No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
235	$-CH_2CH_2-S-CH_2$-3,4-di-($PhCH_2O$-)Ph	-OH
236	$-CH_2CH_2CH_2-S-(CH_2)_8Ph$	-OH
237	$-CH_2CH_2CH_2-S-(CH_2)_8CH_3$	-OH
238	$-CH_2CH_2CH_2-S-(CH_2)_9CH_3$	-OH
239	$-CH_2CH_2CH_2-S-(CH_2)_6Ph$	-OH
240	$-CH_2CH_2CH_2CH_2-S-(CH_2)_7CH_3$	-OH
241	$-CH_2CH_2-S-(CH_2)_6Ph$	-OH
242	$-CH_2CH_2-S-(CH_2)_{10}Ph$	-OH
243	$-CH_2CH_2CH_2-S-CH_2$-4-[$(CH_3)_2CHCH_2$-]Ph	-OH
244	$-CH_2CH_2-S-(CH_2)_3CH=CH(CH_2)_4CH_3$ (*trans*)	-OH
245	$-CH_2CH_2-S-CH_2$-4-[3,4-di-Cl-$PhCH_2O$-]Ph	-OH
246	$-CH_2CH_2CH_2-S-CH_2$-4-[3,4-di-Cl-$PhCH_2O$-]Ph	-OH
247	$-CH_2CH_2-SO$-4-(4-Cl-Ph)-Ph	-OH
248	$-CH_2CH_2CH_2-SO$-4-(4-Cl-Ph)-Ph	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
249	$-CH_2CH_2-S-(CH_2)_{10}CH_3$	-OH
250	$-CH_2CH_2CH_2-S-(CH_2)_{10}CH_3$	-OH
251	$-CH_2CH_2CH_2-S-CH_2$-4-[$CH_3(CH_2)_4O$-]Ph	-OH
252	$-CH_2CH_2CH_2-S-CH_2CH=CH-CH=CH(CH_2)_4CH_3$ (*trans, trans*)	-OH
253	$-CH_2CH_2-S-CH_2$-4-[4-Cl-PhCH_2O-]Ph	-OH
254	$-CH_2CH_2CH_2-S-CH_2$-4-[4-Cl-PhCH_2O-]Ph	-OH
255	$-CH_2CH_2-NH-(CH_2)_9CH_3$	tetrazol-5-yl
256	$-CH_2CH_2-S-(CH_2)_9CH_3$	-*N*-(D-glucosamine)
257	$-CH_2CH_2CH_2-S-CH_2$-4-(4-CF_3-Ph-)Ph	-OH
258	$-CH_2CH_2-S-(CH_2)_9CH_3$	tetrazol-5-yl
259	$-CH_2CH_2CH_2-S-CH_2$-4-(4-F-PhSO_2NH-)Ph	-OH
260	$-CH_2CH_2CH_2-S-(CH_2)_8CH_3$	-OH
261	$-CH_2CH_2CH_2-S(O)-(CH_2)_6Ph$	-OH
262	$-CH_2CH_2-S(O)-(CH_2)_8Ph$	-OH

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}
263	$-CH_2CH_2-S-(CH_2)_3$-4-Cl-Ph	-OH
264	$-CH_2CH_2-S-(CH_2)_6$-4-Cl-Ph	-OH
265	$-CH_2CH_2-SO_2-(CH_2)_9CH_3$	-OH
421	-H	$-NH-CH_2CH_2-NH-(CH_2)_9CH_3$

Ph = phenyl

Table II



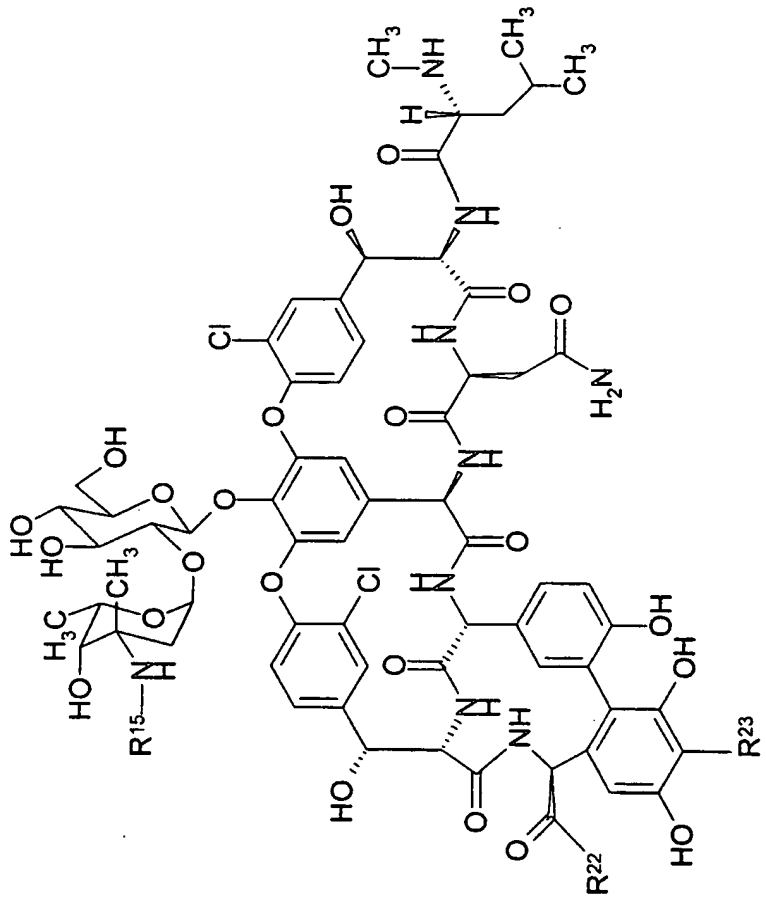
IV

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}	R^{27}
266	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-[CH(OH)]_5CH_2OH$
267	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2CH(OH)CH_2OH$
268	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2CH_2NH_2$
269	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2C(O)OCH_2CH_3$
270	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2COOH$
271	$-CH_2CH_2-NH-(CH_2)_9CH_3$ R^{17} = $-CH_2COOH$	-OH	$-CH_2COOH$
272	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-2-pyridyl
273	$-CH_2CH_2-NH-(CH_2)_8CH_3$	-OH	$-CH_2[CH(OH)]_4COOH$
274	-H	$-NHCH_2C(O)CH_2C(O)N(CH_3)_2$	-H
275	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-3-HOOC-Ph
276	$-CH_2CH_2-N(C(O)CH(NH_2)-(CH_2)_4NH_2)-(CH_2)_9CH_3$ (R isomer)	-OH	$-C(O)CH(NH_2)(CH_2)_4NH_2$ (R isomer)
277	$-CH_2CH_2-NH-(CH_2)_{11}CH_3$	-OH	$-CH_2COOH$
278	$-CH_2CH_2-N(C(O)Ph)-(CH_2)_9CH_3$	-OH	-C(O)Ph

No.	R^{15} (R^{17} = H, unless otherwise indicated)	R^{22}	R^{27}
279	$-CH_2CH_2-N(C(O)CH_2NHC(O)CH_3)-(CH_2)_9CH_3$	-OH	$-C(O)CH_2NHC(O)CH_3$
280	$-CH_2CH_2-S-(CH_2)_3CH=CH(CH_2)_4CH_3$ (*trans*)	-OH	$-CH_2CH_2-S-(CH_2)_3CH=CH(CH_2)_4CH_3$ (*trans*)
281	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_3$

Ph = phenyl

Table III



V

No.	R^{15}	R^{22}	R^{23}
282	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
283	$-CH_2CH_2-NH-CH_2$-4-(4-Cl-Ph)Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
284	$-CH_2CH_2-NH-(CH_2)_8CH(OH)CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
285	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-N-(-D-glucosamine)	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
286	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
287	-H	-OH	$-CH_2-NH-CH_2CH_2-NH-(CH_2)_9CH_3$
288	$-CH_2CH_2-NH-CH_2$-4-(4-Cl-Ph)Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
289	-H	$-NH-(CH_2)_3-N(CH_3)_2$	$-CH_2-NH-CH_2CH_2-NHC(O)-(CH_2)_3COOH$
290	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_9CH_3$
291	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-CH_2CH_2-COOH$
292	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_5-COOH$
293	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-(morpholin-4-yl)
294	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH$
295	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-CH_2CH(OH)CH_2OH$

No.	R^{15}	R^{22}	R^{23}
296	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-N[CH_2CH_2OH]_2$
297	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_3-N(CH_3)_2$
298	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-N[(CH_2)_3-N(CH_3)_2]_2$
299	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_3$-(imidazol-1-yl)
300	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_3$-(morpholin-4-yl)
301	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_4-NHC(NH)NH_2$
302	$-CH_2CH_2-NHSO_2-(CH_2)_7CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
303	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
304	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-NHCH(COOH)CH_2COOH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
305	$-CH_2CH_2-NH-(CH_2)_7CH(OH)CH_2CH_3$	-OH	-3,5-di-HO-4-[$-CH_2$-*N*-(*N*-CH_3-D-glucamine)]Ph
306	$-CH_2CH_2-NH-(CH_2)_{10}OH$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
307	$-CH_2CH_2-NHSO_2$-4-Ph-Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
308	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
309	$-CH_2CH_2-NH-(CH_2)_7CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)

No.	R^{15}	R^{22}	R^{23}
310	$-CH_2CH_2-NH-(CD_2)_9CD_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
311	$-CH_2CH_2-S-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
312	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(2-amino-2-deoxygluconic acid)
313	-H	-OH	$-CH_2-NH-CH_2CH_2-NH-(CH_2)_7CH_3$
314	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NHCH(COOH)CH_2COOH$
315	-H	-OH	$-CH_2-NH-CH_2CH_2-NHSO_2-(CH_2)_7CH_3$
316	-H	-OH	$-CH_2-NH-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$
317	-H	-OH	$-CH_2-NH-CH_2CH_2-NHSO_2-(CH_2)_{11}CH_3$
318	-H	-OH	$-CH_2-NH-CH_2CH_2-NH-(CH_2)_7CH_3$
319	$-CH_2CH_2-SO-(CH_2)_9CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
320	$-CH_2CH_2-NHSO_2-CH_2$-4-(4-Cl-Ph)Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
321	$-CH_2CH_2-NH-CH_2CH=CH-CH=CH(CH_2)_4CH_3$ (*trans, trans*)	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
322	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	-OH	$-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH$
323	$-CH_2CH_2CH_2-NHSO_2-CH_2$-4-(4-Cl-Ph)Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)

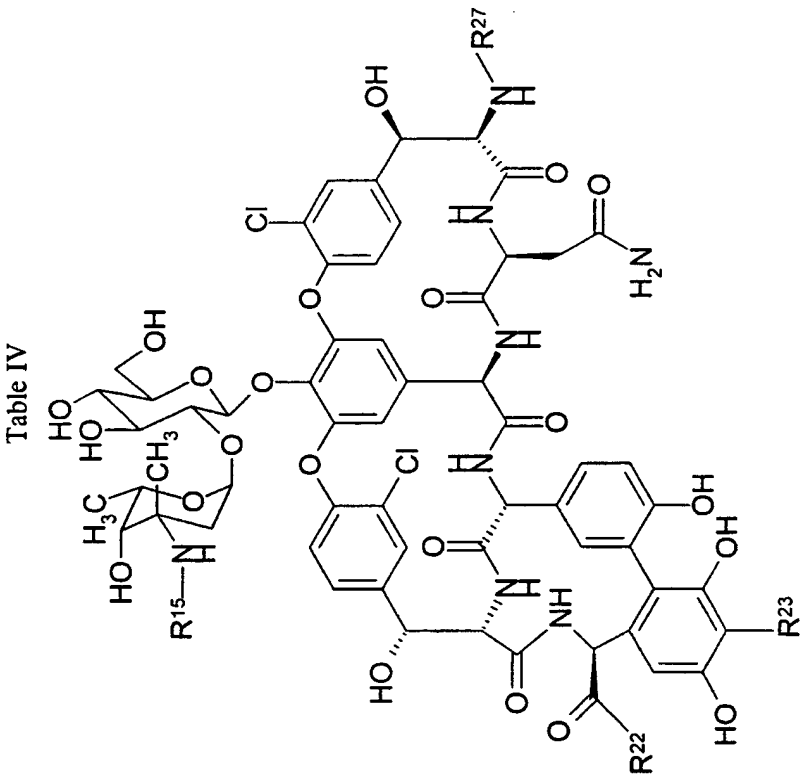
No.	R^{15}	R^{22}	R^{23}
324	$-CH_2CH_2-NH-CH_2$-4-[$(CH_3)_2CHCH_2$-]Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
325	$-CH_2CH_2-NH-CH_2$-4-[$(CH_3)_2CHCH_2$-]Ph	-OH	$-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH$
326	$-CH_2CH_2-NH-CH_2$-4-[4-Cl-$PhCH_2O$-]Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
327	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NHCH_2CH_2C(O)$-*N*-(D-glucosamine)
328	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH$
329	$-CH_2CH_2-NH-(CH_2)_9CH_3$	$-NHCH(COOH)CH_2COOH$	$-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH$
330	$-CH_2CH_2-NH-(CH_2)_{11}CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
331	$-CH_2CH_2CH_2-NH-CH_2$-4-(4-CF_3-Ph)Ph	-OH	$-CH_2-NH-CH_2CH_2-O-CH_2CH_2OH$
332	$-CH_2CH_2CH_2-NH-CH_2$-4-(4-CF_3-Ph)Ph	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
333	$-CH_2CH_2CH_2-NH-CH_2$-4-(4-CF_3-Ph)Ph	-OH	$-CH_2-NH-(CH_2)_3$-(imidazol-1-yl)
334	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	-OH	$-CH_2$-NH-(6-oxo-[1,3]oxazinan-3-yl)
335	$-CH_2CH_2-NH-(CH_2)_8CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)
336	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$	-OH	$-CH_2-NH-(CH_2)_3$-(imidazol-1-yl)
337	-H	-*N*-(D-glucosamine)	$-CH_2-NH-CH_2CH_2-NHSO_2-(CH_2)_{11}CH_3$

No.	R^{15}	R^{22}	R^{23}
338	-H	-OH	$-CH_2-NH-CH_2CH_2-S-(CH_2)_7CH_3$
339	-H	-OH	$-CH_2-NH-CH_2CH_2-S-(CH_2)_8CH_3$
340	-H	-OH	$-CH_2-NH-CH_2CH_2-NHSO_2-(CH_2)_8CH_3$
341	-H	-OH	$-CH_2-NH-CH_2CH_2-S-(CH_2)_9CH_3$
342	-H	-OH	$-CH_2-NH-CH_2CH_2-NHSO_2-(CH_2)_7CH_3$
343	$-CH_2CH_2-NH-CH_2$-4-(4-CF_3-Ph)Ph	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
344	-H	-OH	$-CH_2-NH-CH_2CH_2-S-(CH_2)_{11}CH_3$
345	-H	-OH	$-CH_2-NH-CH_2CH_2-NHSO_2-(CH_2)_{11}CH_3$
346	-H	-OH	$-CH_2-NH-CH_2CH_2-S-(CH_2)_6Ph$
347	-H	-OH	$-CH_2-NH-CH_2CH_2-S-(CH_2)_8Ph$
348	-H	-OH	$-CH_2-NH-CH_2CH_2-S-(CH_2)_{10}Ph$
349	-H	-OH	$-CH_2-NH-CH_2CH_2-S-CH_2$-4-(4-CF_3-Ph)Ph
350	$-CH_2CH_2-S-(CH_2)_8Ph$	-OH	-CH_2-*N*-(*N*-CH_3-D-glucamine)
351	-H	-OH	$-CH_2-NH-CH_2CH_2-SO_2-(CH_2)_{11}CH_3$

No.	R^{15}	R^{22}	R^{23}
352	$-CH_2CH_2-S-(CH_2)_8CH_3$	-OH	$-CH_2$-*N*-(*N*-CH_3-D-glucamine)

Ph = phenyl

Table IV



VI

No.	R^{15} (R^{23} = H, unless otherwise indicated)	R^{22}	R^{27}
353	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-H
354	-H	-OH	$-CH_2CH_2-NH-(CH_2)_9CH_3$
355	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-CH_2CH_2-NH-(CH_2)_9CH_3$
356	$-CH_2CH_2-NH-(CH_2)_9CH_3$ R^{23} = -CH_2-*N*-(*N*-CH_3-D-glucamine)	-OH	-H
357	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-*N*-(D-glucosamine)	-H
358	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-(CH_2)_3CH(CH_3)_2$
359	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2CH_2CH(CH_3)_2$
360	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)(CH_2)_4NH_2$ (R isomer)
361	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)(CH_2)_4NH_2$ (S isomer)
362	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)(CH_2)_2COOH$ (R isomer)
363	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(NH)NH_2$
364	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)CH_2$-(imidazol-4-yl) (R isomer)
365	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)CH_2$-COOH (R isomer)

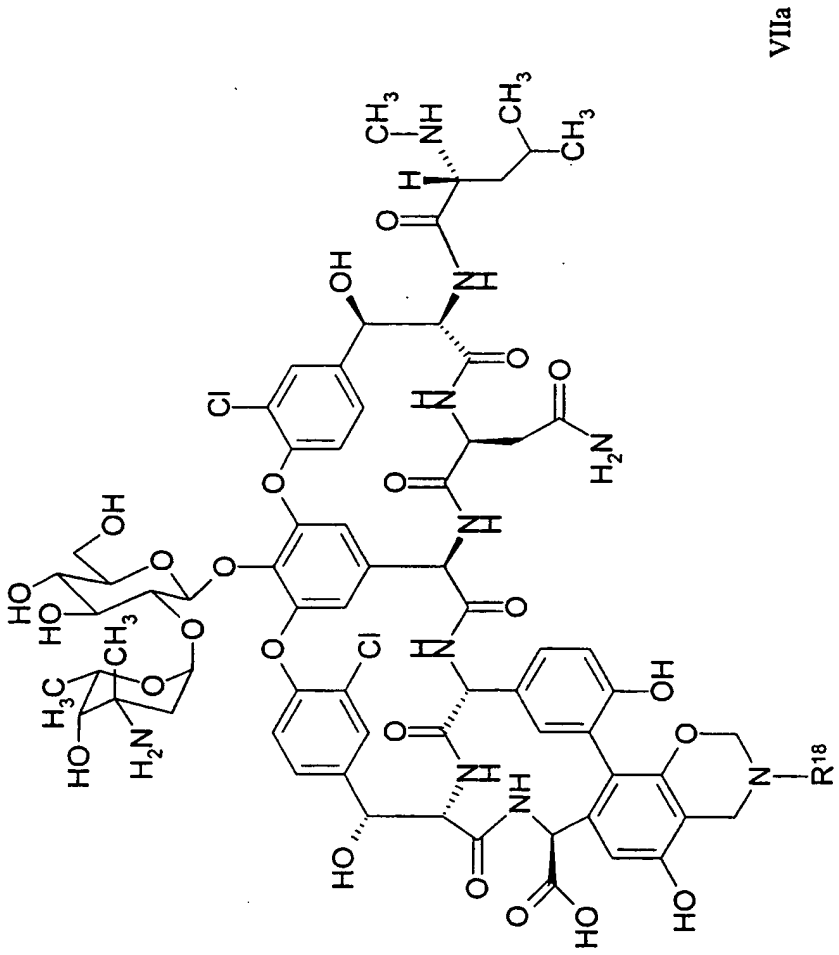
No.	R^{15} (R^{23} = H, unless otherwise indicated)	R^{22}	R^{27}
366	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)CH(CH_3)CH_2CH_3$ (S isomer)
367	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)NHCH_2CH(CH_3)_2$
368	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(NH)CH_2CH(CH_3)_2$
369	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)CH_2$-Ph (R isomer)
370	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2NHCH_3$
371	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)CH_2$-3-HO-Ph
372	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NH_2)CH_2$-3-HO-Ph
373	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-2-[PhCH(CH_3)NHC(O)-]Ph (R isomer)
374	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-[1-PhC(O)-2-oxoimidazolidin-5-yl] (S isomer)
375	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2$-(1-HO-cycloprop-1-yl)
376	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2$-(naphth-2-yl)
377	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)(CH_2)_9$-OH
378	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-2,4-di-HO-Ph
379	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-2,6-di-HO-3-pyridyl

No.	R^{15} (R^{23} = H, unless otherwise indicated)	R^{22}	R^{27}
380	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2-O-CH_2CH_2-O-CH_2CH_2OCH_3$
381	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2CH(Ph)_2$
382	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2$-3-HO-Ph
383	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2-NHC(O)$-3-CH_3-Ph
384	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2CH_2-O$-Ph
385	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2CH_2$-3-pyridyl
386	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2CH_2CH_2$-4-CH_3O-Ph
387	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-(3H-benzotriazol-5-yl)
388	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)$-[1-$(CH_3)_3COC(O)$-pyrrolidin-2-yl) (S isomer)
389	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2CH_2CH_2$-cyclohexyl
390	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-(1H-indol-2-yl)
391	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2NHC(O)$-furan-2-yl
392	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH(NHC(O)CH_3)CH_2$-4-HO-Ph (S isomer)
393	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	$-C(O)CH_2NHC(O)CH=CH$-furan-2-yl (*trans*)

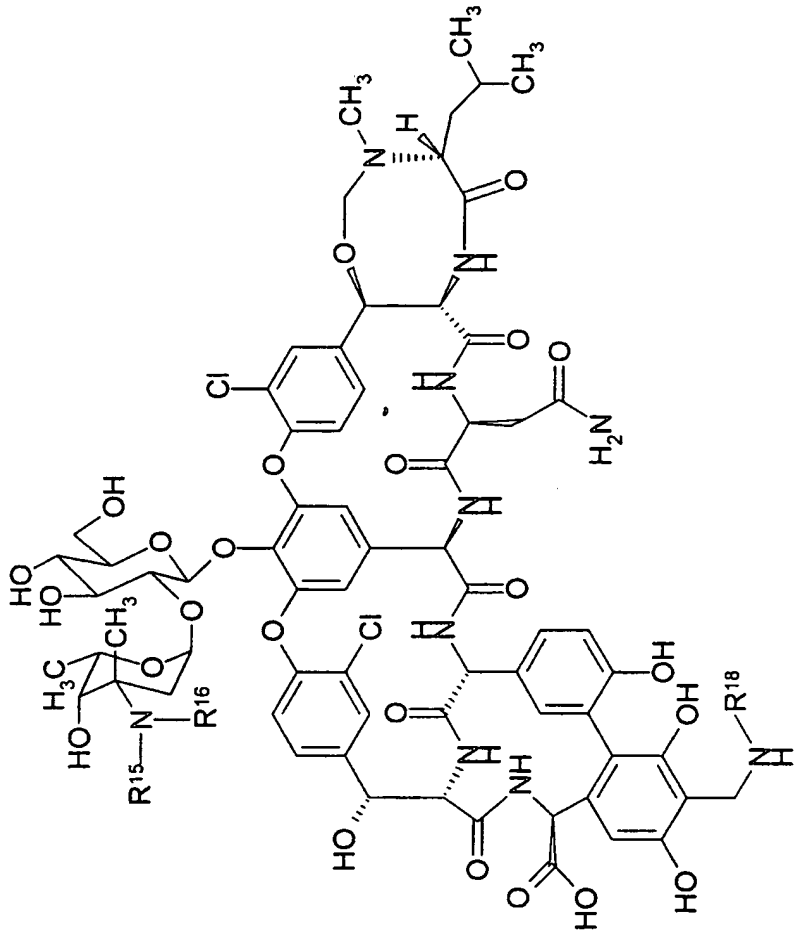
No.	R^{15} (R^{23} = H, unless otherwise indicated)	R^{22}	R^{27}
394	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-(1-CH_3CH_2-7-CH_3-4-oxo-1,4-dihydro[1,8]naphthyridin-3-yl)
395	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-2,3,4,5,6-penta-F-Ph
396	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-(1,3-benzodioxol-5-yl)
397	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)CH_2-(4-oxo-2-thiooxothiazolidin-3-yl)
398	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)-(3,4,5-tri-HO-cyclohex-1-enyl)
399	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)$CH_2CH_2C(O)NH_2$
400	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)CH_2-(5-CH_3-2,4-dioxo-3,4-dihydropyrimidin-1-yl)
401	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH(CH_3)_2$ (R isomer)
402	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH_2C(O)$-(2-H_2N-Ph)
403	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)CH_2-NH_2
404	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)$CH(NHCH_3)CH_2CH(CH_3)_2$ (S isomer)
405	$-CH_2CH_2-NH-(CH_2)_9CH_3$	-OH	-C(O)$CH(NH_2)CH_2CH(CH_3)_2$ (S isomer)

Ph = phenyl

Table V



VIIa



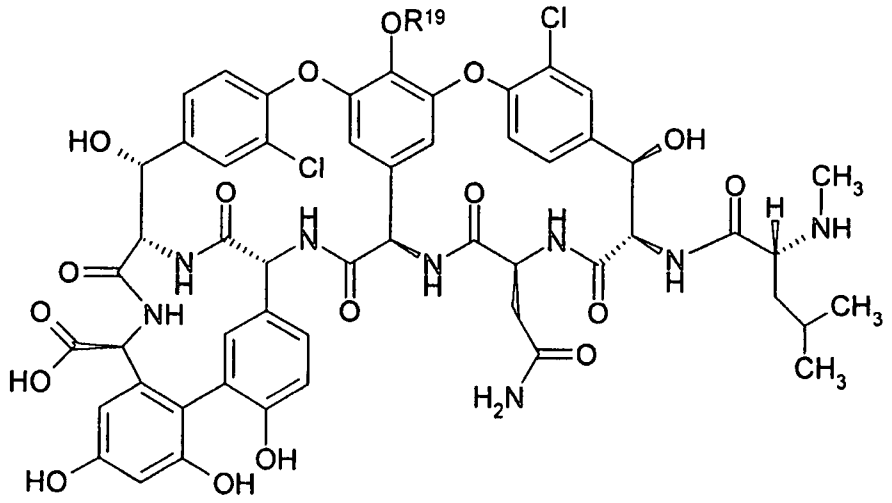
VIIb

and/or

No.	R^{18}
406	$-CH_2CH_2-NHSO_2-(CH_2)_7CH_3$
407	$-CH_2CH_2-NHSO_2-(CH_2)_9CH_3$
408	$-CH_2CH_2-NHSO_2-(CH_2)_{11}CH_3$
409	$-CH_2CH_2-S-(CH_2)_7CH_3CH_2$
410	$-CH_2CH_2-S-(CH_2)_8CH_3$
411	$-CH_2CH_2CH_2-NHSO_2-(CH_2)_9CH_3$
412	$-CH_2CH_2-S-(CH_2)_9CH_3$
413	$-CH_2CH_2CH_2-NHSO_2-(CH_2)_7CH_3$
414	$-CH_2CH_2-S-(CH_2)_{11}CH_3$
415	$-CH_2CH_2-S-(CH_2)_6Ph$
416	$-CH_2CH_2-S-(CH_2)_8Ph$
417	$-CH_2CH_2-S-(CH_2)_{10}Ph$
418	$-CH_2CH_2-S-CH_2$-4-(CF_3-Ph)-Ph

Ph = phenyl

Table VI



VIII

No.	R^{19}
419	$-CH_2CH_2CH_2-NH-(CH_2)_7CH_3$
420	$-CH_2C(O)OC(CH_3)_3$
422	$-CH_2CH_2-NH-(CH_2)_9CH_3$

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel derivatives of glycopeptide antibiotics and to pharmaceutical compositions and methods employing such glycopeptide derivatives. When describing the compounds, compositions and methods of this invention, the following terms have the following meanings, unless otherwise indicated.

Definitions

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above, having from 1 to 8 substituents, preferably 1 to 5 substitutents, and more preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms,

preferably 1-10 carbon atoms, more preferably 1-6 carbon atoms. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), the propylene isomers (e.g., $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures. Additionally, the term substituted alkylene includes alkylene groups in which from 1 to 5 of the alkylene carbon atoms are replaced with oxygen, sulfur or -NR- where R is hydrogen or alkyl. Examples of substituted alkylenes are chloromethylene (-CH(Cl)-), aminoethylene ($-CH(NH_2)CH2-$), 2-carboxypropylene isomers ($-CH_2CH(CO_2H)CH_2-$), ethoxyethyl ($-CH_2CH_2$ O-CH_2CH_2-) and the like.

The term "alkaryl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, alkylene-O-substituted alkyl, substituted alkylene-O-alkyl and substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy ($-CH_2OCH_3$), ethylenemethoxy ($-CH_2CH_2OCH_3$), *n*-propylene-*iso*-propoxy ($-CH_2CH_2CH_2OCH(CH_3)_2$), methylene-*t*-butoxy ($-CH_2-O-C(CH_3)_3$) and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy ($-CH_2SCH_3$), ethylenethiomethoxy ($-CH_2CH_2SCH_3$), *n*-propylene-*iso*-thiopropoxy ($-CH_2CH_2CH_2SCH(CH_3)_2$), methylene-*t*-thiobutoxy ($-CH_2SC(CH_3)_3$) and the like.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl ($-CH=CH_2$), *n*-propenyl ($-CH_2CH=CH_2$), *iso*-propenyl ($-C(CH_3)=CH_2$), and the like.

The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene ($-CH=CH-$), the propenylene isomers (e.g., $-CH_2CH=CH-$ and $-C(CH_3)=CH-$) and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino,

acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl (-C≡CH), propargyl ($-CH_2C\equiv CH$) and the like.

The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene (-C≡C-), propargylene (-CH_2C≡C-) and the like.

The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acylamino" or "aminocarbonyl" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g.,

morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "aminoacyloxy" or "alkoxycarbonylamino" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl,

substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, sulfonamide, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl, -SO_2-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group -NH_2.

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic provided that both R's are not hydrogen.

"Amino acid" refers to any of the naturally occurring amino acids, as well as synthetic analogs and derivatives thereof. α-Amino acids comprise a carbon atom to which is bonded an amino group, a carboxy group, a hydrogen atom, and a distinctive group referred to as a "side chain". The side chains of naturally occurring amino acids are well known in the art and include, for example,

hydrogen (e.g., as in glycine), alkyl (e.g., as in alanine, valine, leucine, isoleucine, proline), substituted alkyl (e.g., as in threonine, serine, methionine, cysteine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, and lysine), alkaryl (e.g., as in phenylalanine and tryptophan), substituted arylalkyl (e.g., as in tyrosine), and heteroarylalkyl (e.g., as in histidine).

The term "carboxyalkyl" or "alkoxycarbonyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

"Haloalkyl" refers to alkyl as defined herein substituted by 1-4 halo groups as defined herein, which may be the same or different. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3-fluorododecyl, 12,12,12-trifluorododecyl, 2-bromooctyl, 3-bromo-6-chloroheptyl, and the like.

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

"Heteroarylalkyl" refers to (heteroaryl)alkyl- where heteroaryl and alkyl are as defined herein. Representative examples include 2-pyridylmethyl and the like.

The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term "heteroarylene" refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl and the like.

The term "heterocycle" or "heterocyclic" refers to a monoradical saturated unsaturated group having a single ring or multiple condensed rings, from 1 to 40

carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

Another class of heterocyclics is known as "crown compounds" which refers to a specific class of heterocyclic compounds having one or more repeating

units of the formula [-$(CH_2$-$)_a$A-] where a is equal to or greater than 2, and A at each separate occurrence can be O, N, S or P. Examples of crown compounds include, by way of example only, [-$(CH_2)_3$-NH-]$_3$, [-$((CH_2)_2$-O$)_4$-$((CH_2)_2$-NH$)_2$] and the like. Typically such crown compounds can have from 4 to 10 heteroatoms and 8 to 40 carbon atoms.

The term "heterocyclooxy" refers to the group heterocyclic-O-.

The term "thioheterocyclooxy" refers to the group heterocyclic-S-.

The term "heterocyclene" refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

The term "oxyacylamino" or "aminocarbonyloxy" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "saccharide group" refers to an oxidized, reduced or substituted saccharide monoradical covalently attached to the glycopeptide or other compound via any atom of the saccharide moiety, preferably via the aglycone carbon atom. Respresentative saccharides include, by way of illustration, hexoses such as D-glucose, D-mannose, D-xylose, D-galactose, vancosamine, 3-desmethyl-vancosamine, 3-epi-vancosamine, 4-epi-vancosamine, acosamine, actinosamine, daunosamine, 3-epi-daunosamine, ristosamine, N-methyl-D-glucamine, D-glucuronic acid, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine, sialyic acid, iduronic acid, L-fucose, and the like; pentoses such as D-ribose or D-arabinose; ketoses such as D-ribulose or D-fructose; disaccharides such as 2-O-(α-L-

vancosaminyl)-β-D-glucopyranose, 2-O-(3-desmethyl-α-L-vancosaminyl)-β-D-glucopyranose, sucrose, lactose, or maltose; derivatives such as acetals, amines, acylated, sulfated and phosphorylated sugars; oligosaccharides having from 2 to 10 saccharide units. For the purposes of this definition, these saccharides are referenced using conventional three letter nomenclature and the saccharides can be either in their open or preferably in their pyranose form.

The term "amino-containing saccharide group" refers to a saccharide group having an amino substituent. Representative amino-containing saccharides include L-vancosamine, 3-desmethyl-vancosamine, 3-epi-vancosamine, 4-epi-vancosamine, acosamine, actinosamine, daunosamine, 3-epi-daunosamine, ristosamine, *N*-methyl-D-glucamine and the like.

The term "spiro-attached cycloalkyl group" refers to a cycloalkyl group attached to another ring via one carbon atom common to both rings.

The term "sulfonamide" refers to a group of the formula $-SO_2NRR$, where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

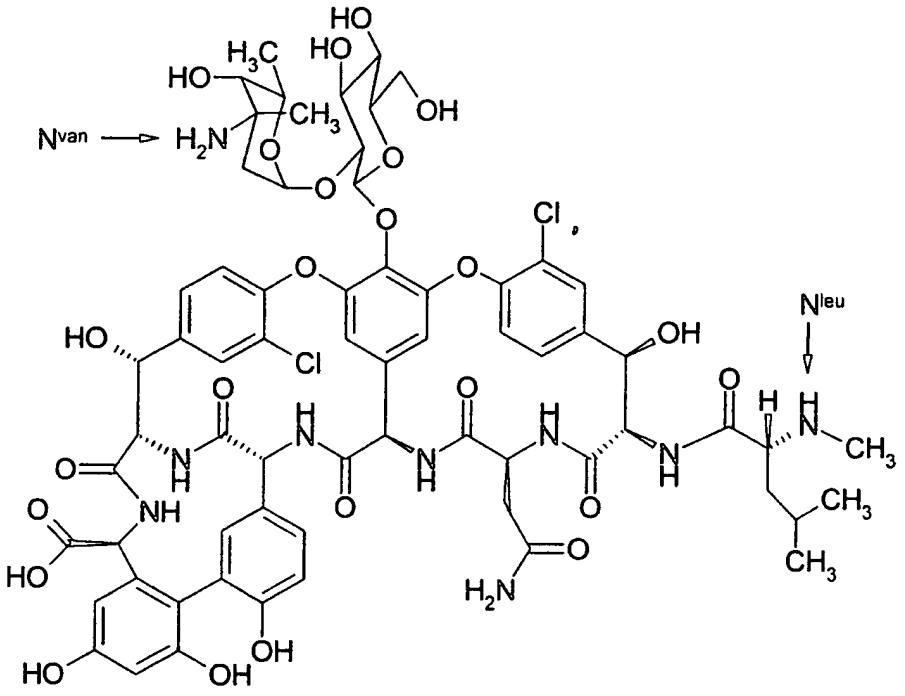
The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

"Glycopeptide" refers to heptapeptide antibiotics, characterized by a multi-ring peptide core optionally substituted with saccharide groups, such as vancomycin. Examples of glycopeptides included in this definition may be found in "Glycopeptides Classification, Occurrence, and Discovery", by Raymond C. Rao and Louise W. Crandall, ("Drugs and the Pharmaceutical Sciences"Volume 63, edited by Ramakrishnan Nagarajan, published by Marcal Dekker, Inc.), which is hereby incorporated by reference in its entirety. Representative glycopeptides include those identified as A477, A35512, A40926, A41030, A42867, A47934, A80407, A82846, A83850 ,A84575, AB-65, Actaplanin, Actinoidin, Ardacin, Avoparcin, Azureomycin, Balhimycin, Chloroorientiein, Chloropolysporin, Decaplanin, *N*-demethylvancomycin, Eremomycin, Galacardin, Helvecardin, Izupeptin, Kibdelin, LL-AM374, Mannopeptin, MM45289, MM47756, MM47761, MM49721, MM47766, MM55260, MM55266, MM55270, MM56597, MM56598, OA-7653, Orenticin, Parvodicin, Ristocetin, Ristomycin, Synmonicin, Teicoplanin, UK-68597, UK-69542, UK-72051, Vancomycin, and the like. The term "glycopeptide" as used herein is also intended to include the general class of peptides disclosed above on which the sugar moiety is absent, i.e. the aglycone series of glycopeptides. For example, removal of the disaccharide moiety appended to the phenol on vancomycin by mild hydrolysis gives

vancomycin aglycone. Also within the scope of the invention are glycopeptides that have been further appended with additional saccharide residues, especially aminoglycosides, in a manner similar to vancosamine.

"Vancomycin" refers to a glycopeptide antibiotic having the formula:



When describing vancomycin derivatives, the term "N^{van}-" indicates that a substituent is covalently attached to the amino group of the vacosamine moiety of vacomycin. Similarly, the term "N^{leu}-" indicates that a substituent is covalently attached to the amino group of the leucine moiety of vancomycin.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For

example, "optionally substituted" means that a group may or may not be substituted with the described substitutent.

"Transglycosylase enzyme substrate" as used herein denotes the molecular target of the transglycosylase enzyme. The substrate binds to the enzyme and eventually results in synthesis of the bacterial cell wall. The action of this enzyme is inhibited by a ligand domain that binds to the enzyme substrate. A ligand such as vancomycin binds to this substrate and in effect "sequesters" the substrate to prevent its recognition by the enzyme and subsequent use in the construction of the bacterial cell wall.

"Potency" as used herein refers to the minimum concentration at which a compound or ligand is able to achieve a desirable biological or therapeutic effect. The potency of a compound or ligand is typically proportional to its affinity for its binding site. In some cases, the potency may be non-linearly correlated with its affinity

As used herein, the terms "inert organic solvent" or "inert solvent" or "inert diluent" mean a solvent or diluent which is essentially inert under the conditions of the reaction in which it is employed as a solvent or diluent. Representative examples of materials which may be used as inert solvents or diluents include, by way of illlustration, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform ("$CHCl_3$"), methylene chloride (or dichloromethane or "CH_2C1_2), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

"Pharmaceutically acceptable salt" means those salts which retain the biological effectiveness and properties of the parent compounds and which are not biologically or otherwise harmful as the dosage administered. The compounds of this invention are capable of forming both acid and base salts by virtue of the presence of amino and carboxyl groups respectively.

Pharmaceutically acceptable base addition salts may be prepared from inorganic and organic bases. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethyl amine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, and N-ethylpiperidine. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example carboxylic acid amides, including carboxamides, lower alkyl carboxamides, di(lower alkyl) carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The compounds of this invention typically contain one or more chiral centers. Accordingly, this invention is intended to include racemic mixtures, diasteromers, enantiomers and mixture enriched in one or more steroisomer. The scope of the invention as described and claimed encompasses the racemic forms of the compounds as well as the individual enantiomers and non-racemic mixtures thereof.

The term "treatment" as used herein includes any treatment of a condition or disease in an animal, particularly a mammal, more particularly a human, and includes:

(i) preventing the disease or condition from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, i.e. arresting its development; relieving the disease or condition, i.e. causing regression of the condition; or. relieving the conditions caused by the disease, i.e. symptoms of the disease.

The term "disease state which is alleviated by treatment with a broad spectrum antibacterial" as used herein is intended to cover all disease states which are generally acknowledged in the art to be usefully treated with a broad spectrum antibacterial in general, and those disease states which have been found to be usefully treated by the specific antibacterials of this invention. Such disease states include, but are not limited to, treatment of a mammal afflicted with pathogenic bacteria, in particular staphylococci (methicillin sensitive and resistant), streptococci (penicillin sensitive and resistant), enterococci (vancomycin sensitive and resistant), and Clostridium difficile

The term "therapeutically effective amount" refers to that amount which is sufficient to effect treatment, as defined herein, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending on the subject and disease state being treated, the severity of the affliction and the manner of administration, and may be determined routinely by one of ordinary skill in the art.

The term "protecting group" or "blocking group" refers to any group which, when bound to one or more hydroxyl, thiol, amino, carboxyl or other groups of the compounds, prevents undesired reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thio, amino, carboxyl or other group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, t-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product. Protecting groups are disclosed in more detail in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis" 2nd Ed., 1991, John Wiley and Sons, N.Y.

Preferred removable amino blocking groups include conventional substituents such as t-butyoxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), fluorenylmethoxycarbonyl (FMOC), allyloxycarbonyl (ALOC) and the like, which can be removed by conventional conditions compatible with the nature of the product.

Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild conditions compatible with the nature of the product.

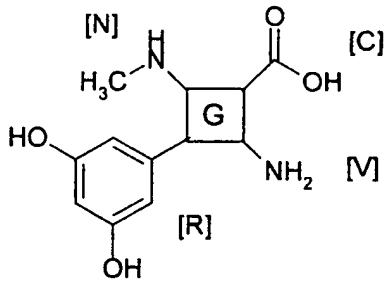
"Biological effect" as used herein includes, but is not limited to, increased affinity, increased selectivity, increased potency, increased efficacy, increased duration of action, decreased toxicity, and the like.

General Synthetic Procedures

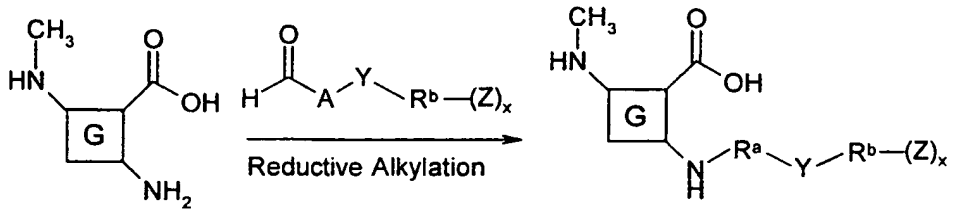
The glycopeptide compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

In the following reaction schemes, the glycopeptide compounds are depicted in a simplified form as a box "G" that shows the carboxy terminus labeled [C], the vancosamine amino terminus labeled [V], the "non-saccharide" amino terminus (leucine amine moiety) labeled [N], and optionally, the resorcinol moiety labeled [R] as follows:



In one preferred embodiment, the glycopeptide compounds of the present invention are prepared by reductive alkylation of a glycopeptide as shown in the following reaction:



where A represents R^a minus one carbon atom and R^a, R^b, Y, Z and *x* are as defined herein. This reaction is typically conducted by first contacting one equivalent of a glycopeptide, such as vancomycin, with an excess, preferably from 1.1 to 1.3 equivalents, of the desired aldehyde in the presence of an excess, preferably about 2.0 equivalents, of a tertiary amine, such as diisopropylethylamine (DIPEA) and the like. This reaction is typically conducted in an inert diluent, such as DMF, at ambient temperature for about 1 to 2 hours until formation of the corresponding imine and/or hemiaminal is substantially complete. The resulting imine and/or hemiaminal is typically not isolated, but is reacted *in situ* with a metal hydride reducing agent, such as sodium cyanoborohydride and the like, to afford the corresponding amine. This reaction

is typically conducted by contacting the imine and/or hemiaminal with about 1 to 1.2 equivalents of the reducing agent at ambient temperature in methanol in the presence of an excess, preferably about 3 equivalents, of trifluoroacetic acid. The resulting alkylated product is readily purified by conventional procedures, such as reverse-phase HPLC. Surprisingly, by forming the imine and/or hemiaminal in the presence of a trialkyl amine, the selectivity for the reductive alkylation reaction is greatly improved, i.e., reductive alkylation at the amino group of the saccharide (e.g., vancosamine) is favored over reductive alkylation at the N-terminus (e.g., the leucinyl group) by at least 10:1, more preferably 20:1.

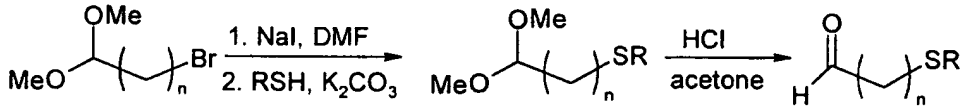
If desired, the glycopeptide compounds of this invention can also be prepared in a step-wise manner in which a precursor to the $-R^a-Y-R^b-(Z)_x$ group is first attached the glycopeptide by reductive alkylation, followed by subsequent elaboration of the attached precursor using conventional reagent and procedures to form the $-R^a-Y-R^b-(Z)_x$ group as illustrated below. Additionally, ketones may also be employed in the above-described reductive alkylation reactions to afford α-substituted amines.

Any glycopeptide having an amino group may be employed in these reductive alkylation reactions. Such glycopeptides are well-known in the art and are either commercially available or may be isolated using conventional procedures. Suitable glycopeptides are disclosed, by way of example, in U.S. Patent Nos. 3,067,099; 3,338,786; 3,803,306; 3,928,571; 3,952,095; 4,029,769; 4,051,237; 4,064,233; 4,122,168; 4,239,751; 4,303,646; 4,322,343; 4,378,348; 4,497,802; 4,504,467; 4,542,018; 4,547,488; 4,548,925; 4,548,974; 4,552,701; 4,558,008; 4,639,433; 4,643,987; 4,661,470; 4,694,069; 4,698,327; 4,782,042; 4,914,187; 4,935,238; 4,946,941; 4,994,555; 4,996,148; 5,187,082; 5,192,742; 5,312,738; 5,451,570; 5,591,714; 5,721,208; 5,750,509; 5,840,684; and 5,843,889; the disclosures of which are incorporated herein by reference in their

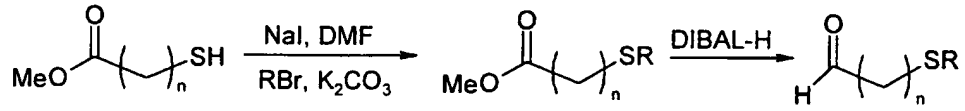
entirety. Preferably, the glycopeptide employed in the above reaction is vancomycin.

The aldehydes and ketones employed in the reactive alkylation reaction are also well-known in the art and are either commercially available or can be prepared by conventional procedures using commercially available starting materials and conventional reagents. Typically, such materials are prepared by conventional coupling of, for example, functionalized acetals having an amino, thiol, hydroxyl, halo or other substitutent, with an suitable intermediate having a complementary functional group to form sulfides, ethers, amines, sulfonamides and the like. Subsequent hydrolysis of the acetal affords the corresponding aldehyde. Such reactions are well-known in the art and are described, for example, in March, *Advanced Organic Chemistry*, Fourth Edition, John Wiley & Sons, New York (1992), and references cited therein. Representative synthesis of aldehyde compounds are illustrated in Schemes 1-5:

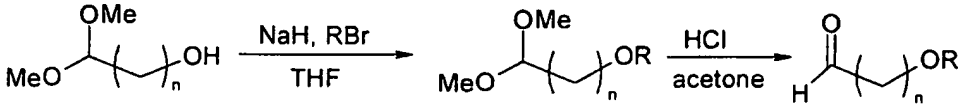
Scheme 1



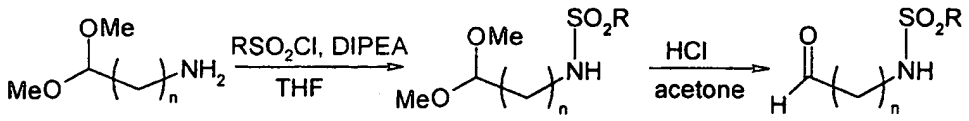
Scheme 2



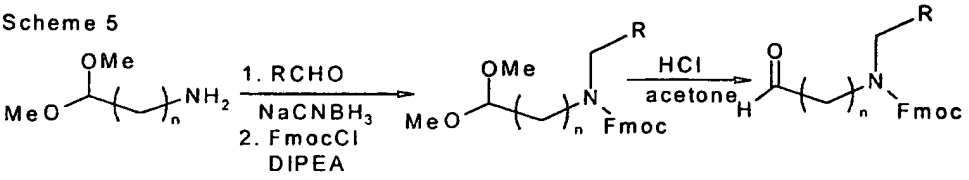
Scheme 3



Scheme 4



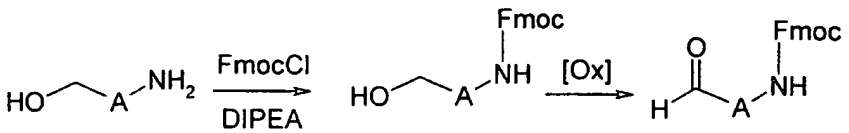
Scheme 5



where R represents -R^b-$(Z)_x$ or -(R^b minus one carbon atom)-$(Z)_x$ (where R^b, Z and x are as defined herein).

By way of further illustration, the following schemes describe the synthesis of representative starting materials and compounds of this invention. For example, Scheme A illustrates a method for preparing an Fmoc-aminoaldehyde **5** from the corresponding aminoalcohol **3**, where A is as defined herein. In this reaction, the aminoalcohol is protected by conventional techniques, for example, by treatment with 9-fluorenylmethyl chloroformate in the presence of base, to yield the Fmoc-protected aminoalcohol **4**. Oxidation by known techniques then provides the aldehyde **5**.

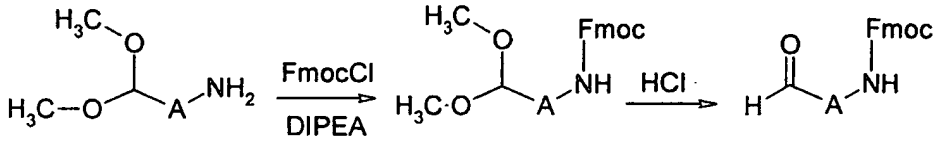
Scheme A



3 **4** **5**

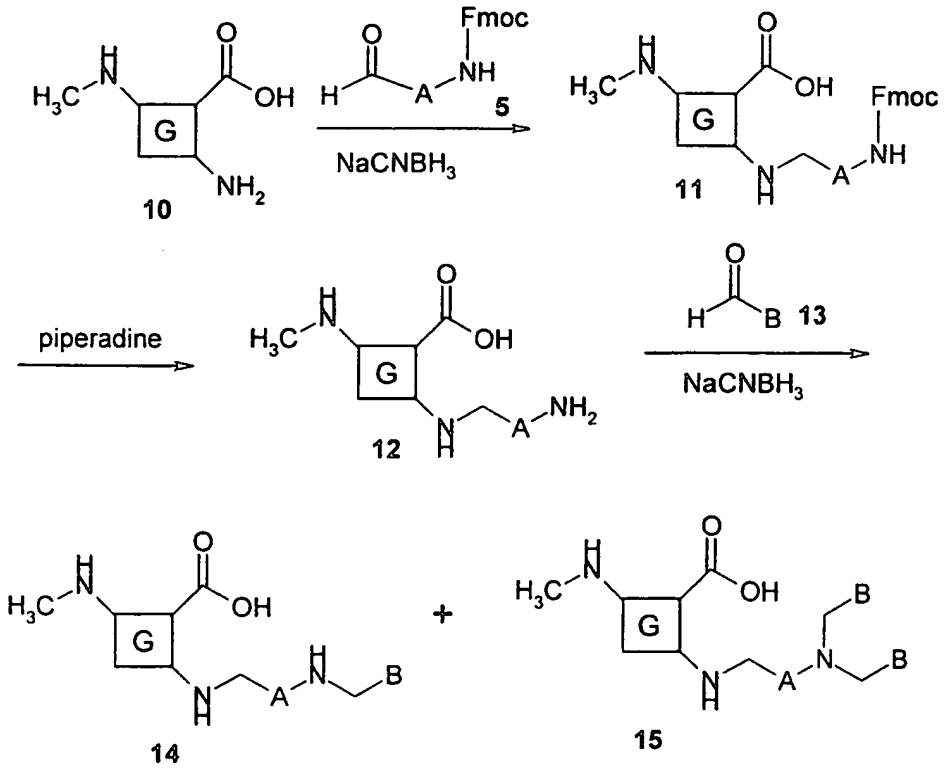
Scheme B illustrates an alternate route to F-moc- protected aminoaldehyde **5**. This route is described in further detail in Sasake, Y., Abe, *J. Chem. Pharm. Bull.* (1997), *45(1)*, 13-17.

Scheme B



The Fmoc-protected aminoaldehyde of formula **5** can then be reacted with a glycopeptide, for example vancomycin, as shown in Scheme C.

Scheme C

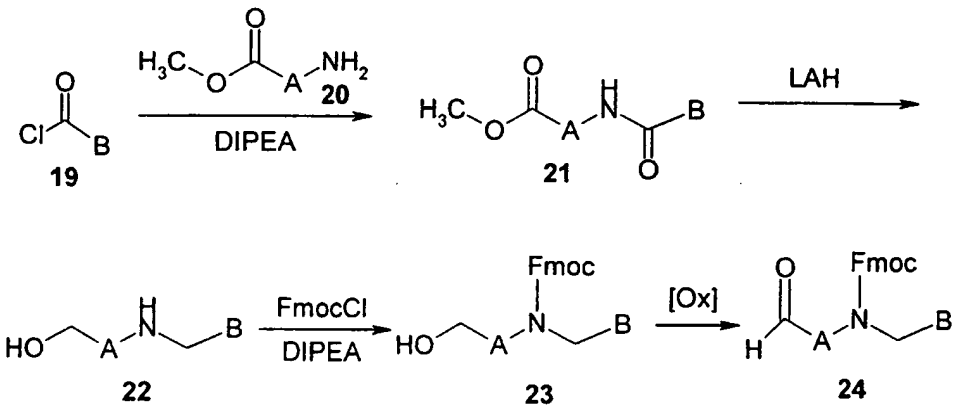


where B represents -(R^b minus one carbon atom)-$(Z)_x$, where R^b, Z and x are as defined herein.

This reaction is conducted under reductive alkylation conditions to yield a glycopeptide intermediate **11**. Deprotection of **11** with piperidine yields the corresponding the glycopeptide **12** having a primary amino group. Reaction of **12** with aldehyde **13** under standard reductive alkylation conditions gives glycopeptide derivative **14** and the corresponding bis-adduct **15**, which are separated by conventional techniques, such as HPLC.

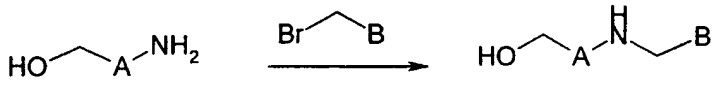
Scheme D illustrates a method for preparing an Fmoc protected aminoaldehyde **24**. In this scheme, reaction of acid chloride **19** with aminoester **20** under conventional amide coupling conditions gives amidoester **21**. Reduction of the both the ester and amide moieties using a metal hydride reducing agent, such as lithium aluminum hydride (LAH) gives aminoalcohol **22**. Protection and oxidation, as in Scheme A, yields an aldehyde of formula **24**.

Scheme D



Alternatively, aldehyde **24** can be prepared as shown in Scheme D'. In this reaction, direct alkylation of amino alcohol **3** under conventional amine alkylation conditions gives amino alcohol **22**, which can then be used as described above in Scheme D.

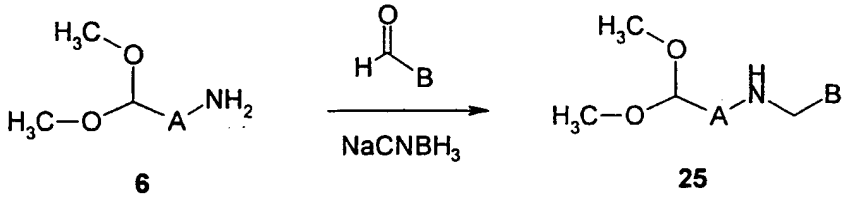
Scheme D'



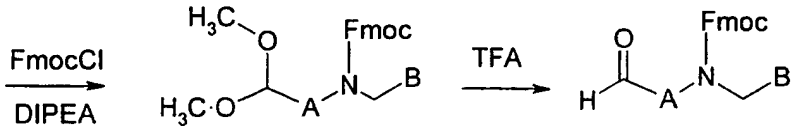
3 **22**

Scheme E illustrates an alternative method for preparing aldehyde **24**. In this reaction, amino acetal **6** is reductively alkylated to provide **25**. Subsequent protection of the amino group and hydrolysis of the acetal under conventional conditions then provides aldehyde **24**.

Scheme E



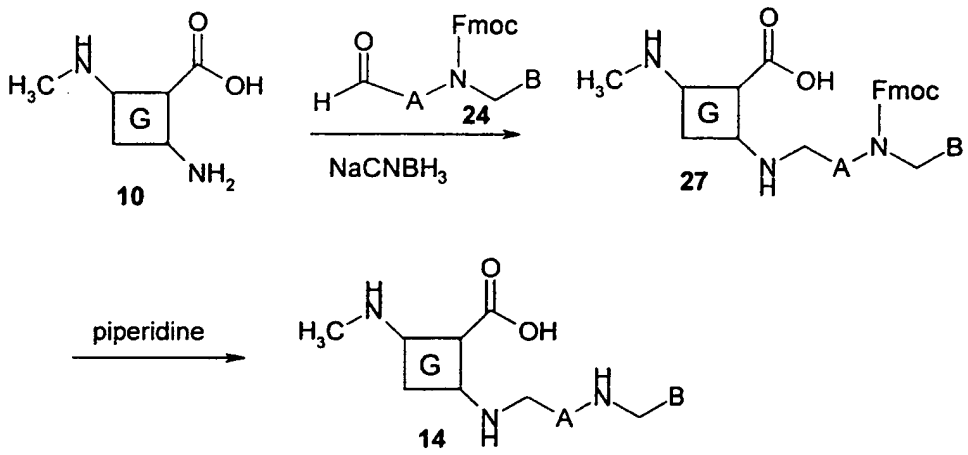
6 **25**



26 **24**

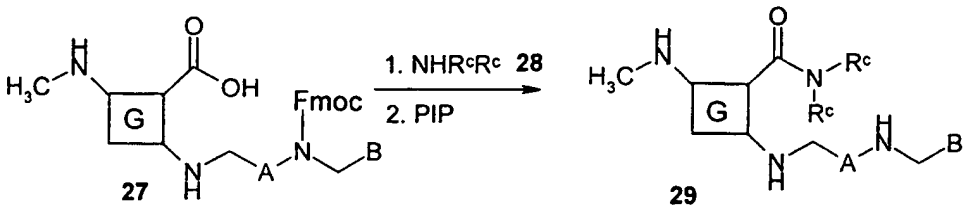
Scheme F illustrates another method for reductive alkylation of a glycopeptide. In this scheme, Fmoc-protected aldehyde **24**, prepared as descrubed above, is reacted with a glycopeptide **10**, such as vancomycin, under reductive alkylation conditions to afford glycopeptide derivative **27**. Subsequent deprotection with piperidine provides glycopeptide derivative **14**.

Scheme F



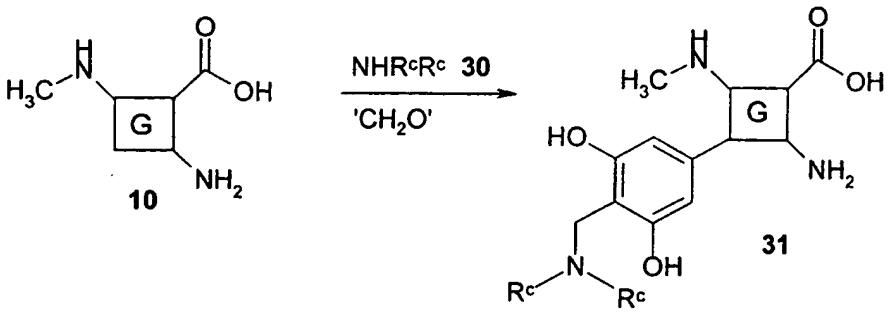
Scheme G illustrates the conversion of the carboxyl group of a glycopeptide derivative, such as vancomycin, into an amide. In this reaction, amine **28** is reacted with a glycopeptide derivative, such as **27**, under standard peptide coupling conditions, for example, PyBOP and HOBT in DMF, to provide amide **29**, after deprotection.

Scheme G



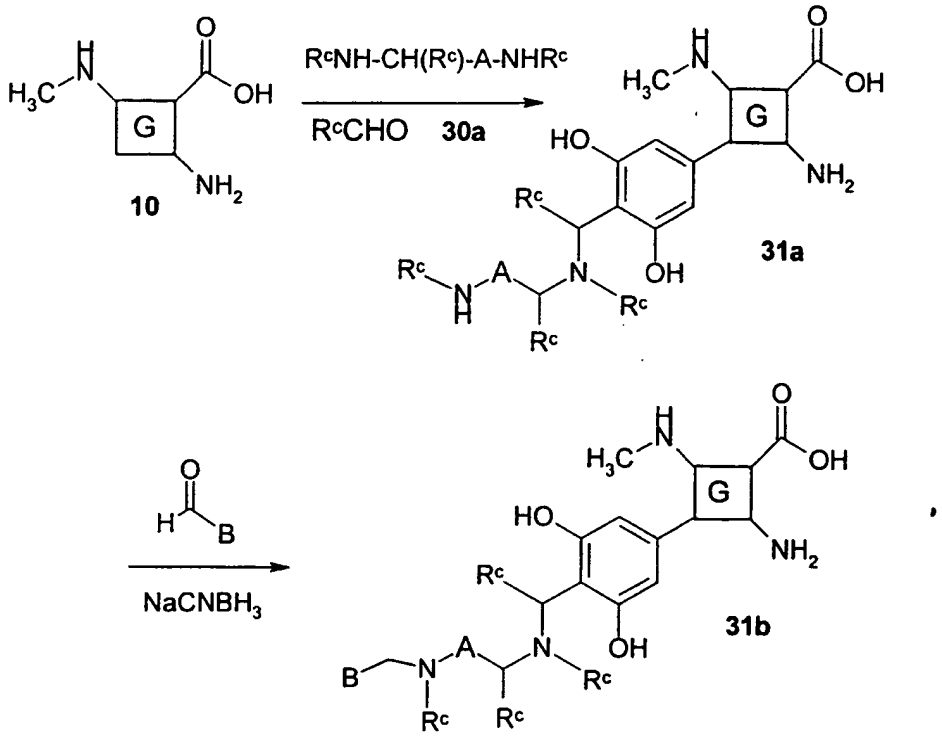
Scheme H illustrates the introduction of an aminoalkyl sidechain at the resorcinol moiety of a glycopeptide, such as vancomycin, via a Mannich reaction. In this reaction, amine **30** and an aldehyde, such as formalin (a source of formaldehyde), are reacted with the glycopeptide under basic conditions to give the glycopeptide derivative **31**.

Scheme H



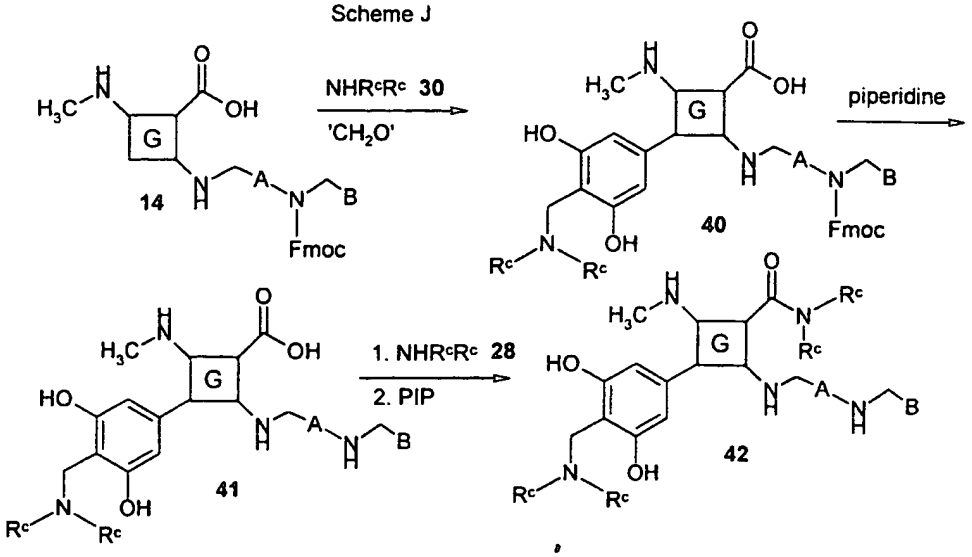
Similarly, Scheme I illustrates a introduction of a substituent of the formula $-R^a-Y-R^b-(Z)_x$ at the resorcinol moiety of a glycopeptide using the Mannich reaction. In these reactions, excess aldehyde, such as formaldehyde, can react to afford the cyclized compounds of formula VIIa and/or VIIb.

Scheme I



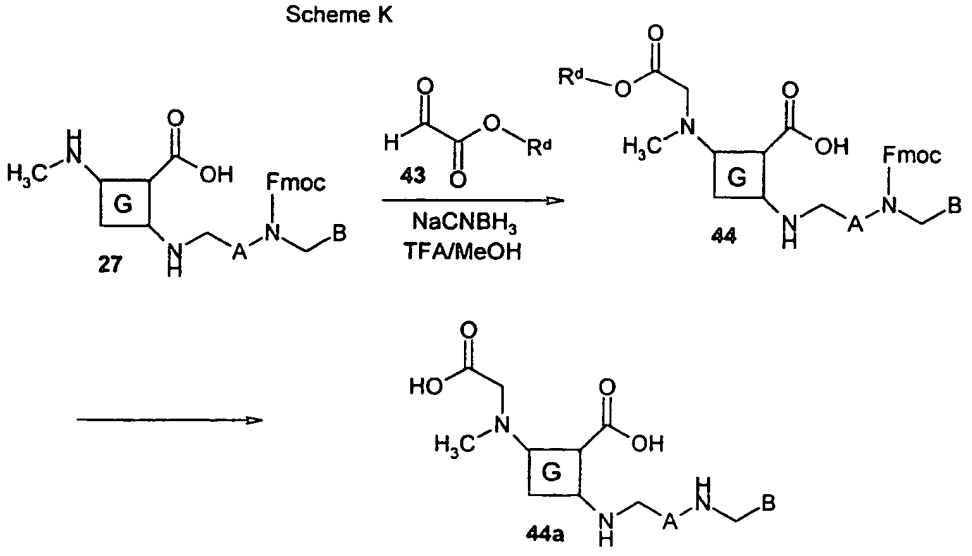
Scheme J illustrates a synthesis of a glycopeptide derivative using several of the reactions described above. In this scheme, glycopeptide derivative **27** is derivatized at the resorcinol moiety using the Mannich reaction described in Scheme H to provide glycopeptide derivative **40**. Deprotection and amide coupling at the carboxyl group, as described in Scheme G, affords glycopeptide derivative **42**.

Scheme J



Scheme L illustrates multiple reductive alkylation reaction of a glycopeptide derivative **27** to afford glycopeptide derivative **44a**.

Scheme K



Additional details and other methods for preparing the compounds of this invention are described in the Examples below.

Pharmaceutical Compositions

This invention also includes pharmaceutical composition containing the novel glycopeptide compounds of this invention. Accordingly, the glycopeptide compound, preferably in the form of a pharmaceutically acceptable salt, can be formulated for oral or parenteral administration for the therapeutic or prophylactic treatment of bacterial infections.

By way of illustration, the glycopeptide compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers, and the like. Such pharmaceutical compositions will contain from about 0.1 to about 90% by weight of the active compound, and more generally from about 10 to about 30%. The pharmaceutical compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid. Disintegrators commonly used in the formulations of this invention include croscarmellose, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid.

A liquid composition will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s), for example ethanol, glycerine, sorbitol, non-aqueous solvent such as polyethylene glycol, oils or water, with a suspending agent, preservative, surfactant, wetting agent, flavoring or coloring agent. Alternatively, a liquid formulation can be prepared from a reconstitutable powder.

For example a powder containing active compound, suspending agent, sucrose and a sweetener can be reconstituted with water to form a suspension; and a syrup can be prepared from a powder containing active ingredient, sucrose and a sweetener.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid compositions. Examples of such carriers include magnesium stearate, starch, lactose, sucrose, microcrystalline cellulose and binders, for example polyvinylpyrrolidone. The tablet can also be provided with a color film coating, or color included as part of the carrier(s). In addition, active compound can be formulated in a controlled release dosage form as a tablet comprising a hydrophilic or hydrophobic matrix.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, for example by incorporation of active compound and excipients into a hard gelatin capsule. Alternatively, a semi-solid matrix of active compound and high molecular weight polyethylene glycol can be prepared and filled into a hard gelatin capsule; or a solution of active compound in polyethylene glycol or a suspension in edible oil, for example liquid paraffin or fractionated coconut oil can be prepared and filled into a soft gelatin capsule.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, poly-vinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose. Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used. Additionally, it may be desirable to add a coloring

agent to make the dosage form more attractive in appearance or to help identify the product.

The compounds of the invention and their pharmaceutically acceptable salts that are active when given parenterally can be formulated for intramuscular, intrathecal, or intravenous administration.

A typical composition for intra-muscular or intrathecal administration will consist of a suspension or solution of active ingredient in an oil, for example arachis oil or sesame oil. A typical composition for intravenous or intrathecal administration will consist of a sterile isotonic aqueous solution containing, for example active ingredient and dextrose or sodium chloride, or a mixture of dextrose and sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus dextrose injection, Normosol-M and dextrose, Isolyte E, acylated Ringer's injection, and the like. Optionally, a co-solvent, for example polyethylene glycol, a chelating agent, for example ethylenediamine tetracetic acid, and an anti-oxidant, for example, sodium metabisulphite may be included in the formulation. Alternatively, the solution can be freeze dried and then reconstituted with a suitable solvent just prior to administration.

The compounds of the invention and their pharmaceutically acceptable salts which are active on rectal administration can be formulated as suppositories. A typical suppository formulation will generally consist of active ingredient with a binding and/or lubricating agent such as a gelatin or cocoa butter or other low melting vegetable or synthetic wax or fat.

The compounds of this invention and their pharmaceutically acceptable salts which are active on topical administration can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions

include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference in its entirety. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Suitable doses are in the general range of from 0.01-100 mg/kg/day, preferably 0.1-50 mg/kg/day. For an average 70 kg human, this would amount to 0.7 mg to 7g per day, or preferably 7 mg to 3.5g per day.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences,* Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

The following formulation examples illustrate representative pharmaceutical compositions of the present invention.

Formulation Example A

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	200
Lactose, spray-dried	148
Magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Formulation Example B

This example illustrates the preparation of another representative pharmaceutical composition for oral administration of a compound of this invention:

Ingredients	Quantity per tablet, (mg)
Active Compound	400
Cornstarch	50
Lactose	145
Magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

Formulation Example C

This example illustrates the preparation of a representative pharmaceutical composition for oral administration of a compound of this invention.

An oral suspension is prepared having the following composition.

Ingredients	
Active Compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.1 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Formulation Example D

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this invention.

An injectable preparation buffered to a pH of 4 is prepared having the following composition:

Ingredients	
Active Compound	0.2 g
Sodium Acetate Buffer Solution (0.4 M)	2.0 mL
HCl (1N)	q.s. to pH 4
Water (distilled, sterile)	q.s. to 20 mL

Formulation Example E

This example illustrates the preparation of a representative pharmaceutical composition for injection of a compound of this invention.

A reconstituted solution is prepared by adding 20 mL of sterile water to 1 g of the compound of this invention. Before use, the solution is then diluted with 200 mL of an intravenous fluid that is compatible with the active compound. Such fluids are chosen from 5% dextrose solution, 0.9% sodium chloride, or a mixture of 5% dextrose and 0.9% sodium chloride. Other examples are lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, Normosol-M and 5% dextrose, Isolyte E, and acylated Ringer's injection

Formulation Example F

This example illustrates the preparation of a representative pharmaceutical composition for topical application of a compound of this invention.

Ingredients	grams
Active compound	0.2-10
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water q.s. to 100	

All of the above ingredients, except water, are combined and heated to 60°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

Formulation Example G

This example illustrates the preparation of a representative pharmaceutical composition containing a compound of this inventon.

A suppository totaling 2.5 grams is prepared having the following composition:

Ingredients	
Active Compound	500 mg
Witepsol H-15*	balance

(*triglycerides of saturated vegetable fatty acid; a product of Riches-Nelson, Inc., New York, N.Y.)

Utility

The glycopeptide compounds of this invention, and their pharmaceutically acceptable salts, are useful in medical treatments and exhibit biological activity, including antibacterial activity, which can be demonstrated in the tests described in the Examples. Such tests are well known to those skilled in the art, and are referenced and described in Lorian "Antibiotics in Laboratory Medicine", Fourth Edition, Williams and Wilkins (1991), which is hereby incorporated by reference.

Accordingly, this invention provides methods for treating infectious diseases, especially those caused by Gram-positive microorganisms, in animals. The compounds of this invention are particularly useful in treating infections caused by methicillin-resistant staphylococci. Also, the compounds are useful in treating infection due to enterococci, including vancomycin-resistant enterococci (VRE). Examples of such diseases are severe staphylococcal infections, for example, staphylococcal endocarditis and staphylococcal septicemia. The animal may be either susceptible to, or infected with, the microorganism. The method comprises administering to the animal an amount of a compound of this invention which is effective for this purpose. In general, an effective amount of a compound of this invention is a dose between about 0.5 and about 100 mg/kg. A preferred

dose is from about 1 to about 60 mg/kg of active compound. A typical daily dose for an adult human is from about 50 mg to about 5 g.

In practicing this method, the antibiotic can be administered in a single daily dose or in multiple doses per day. The treatment regimen may require administration over extended periods of time, for example, for several days or for from one to six weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms in the infection.

Among other properties, the compounds of this invention have also been found to be more chemically stable compared to N-acyl glycopeptide derivatives. More specifically, it has been observed that acylation of the amino group of the vancosamine moiety of vancomycin increases the rate of hydrolysis of the disaccharide moiety. In contrast, when the compounds of this invention are substituted on the amino group of the vancosamine moiety of vancomycin with a $-R^a-Y-R^b-(Z)_x$ group, no increase in the rate of hydrolysis of the disaccharide moiety is observed.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

EXAMPLES

In the examples below, the following abbreviations have the following meanings. Any abbreviations not defined have their generally accepted meaning. Unless otherwise stated, all temperatures are in degrees Celsius.